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Original Article

Risk factors for renal damage in Henoch-Schonlein purpura: a meta analysis

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Abstract: Purpose: It is well-documented that renal damage often occurs in Henoch-Schonlein purpura (HSP). We aimed to investigate the risk factors for the onset of renal damage of HSP. Methods: According to a predefined searching criterion, we searched for the association studies regarding the comparisons between HSP and Henoch-Schonlein purpura nephritis (HSPN) through February 2015. Standard mean difference (SMD) and confidence intervals (CI) were calculated. Results: Age, SBP, C3, Hb, and BUN were significantly lower in HSP compared with those in HSPN ($P \leq 10^{-4}$, 0.034, 0.034, 0.040, and 0.048, respectively). ALB was markedly higher in HSP in comparison to that in HSPN (P = 0.010). No obvious differences of WBC, PLT, IgA, IgG, IgM and Scr between HSP and HSPN were noted. Conclusions: Our findings indicate that elevated age, SBP, C3, Hb, and BUN and decreased ALB are risk factors for renal damage onset in HSP patients.

Keywords: Risk factors, renal damage, Henoch-Schonlein purpura

Introduction

Henoch-Schonlein purpura (HSP) is a self-limited vasculitis occurring mostly in children [1]. HSP is a multisystem disease affecting skin, joints, gastrointestinal tract, and kidneys [2]. Renal damage is the most common and severe complication of HSP [3]. The long-term prognosis of HSP depends mainly on the severity of renal damage, which is also called Henoch-Schonlein purpura nephritis (HSPN) [3]. The ratio of HSPN in HSP patients varies widely among different people. Meanwhile, the severity of HSPN also varies significantly different among HSP patients. Some HSP cases present with microhaematuria, while some progress to chronic kidney diseases, even end-stage renal diseases [4]. In terms of the great harms of renal damage of HSP, effective prevention of HSPN and appropriate evaluation of renal damage of HSP seem very important.

Recently, a number of studies have been focused on the risk factors for the onset/severity of HSPN. Some molecules are regarded to be related with the onset of HSPN [5]. Some genetic factors, such as genetic polymorphisms are confirmed to be associated with the onset of HSPN [6, 7]. On the other hand, the pathological changes of kidney are often regarded as the gold standard of severity of HSPN. However, in certain instances, the renal biopsy cannot be performed, and some laboratory testing cannot be conducted in many institutions. Hence, to search for simple and relative non-invasive indexes to evaluate and reduce the renal damage of HSP is of great clinical implications.

Many common factors are closely associated with the renal damage. For example, HSP often occurs in children aged < 5 years, most HSP patients aged between 4 and 6 years [8]. Age is a possible risk factor for renal damage of HSP. Obesity is also a risk factor for renal damage [9]. Waist-to-height ratio is independently associated with CKD in overweight type 2 diabetic patients [10]. Proteinuria is a marker of renal disease and is also well recognized as an independent factor for renal tubular and tubulointerstitial lesions, which further promotes the progression of kidney injury and the loss of renal function [11].

In this study, we performed a meta-analysis of the previous publications regarding the com-

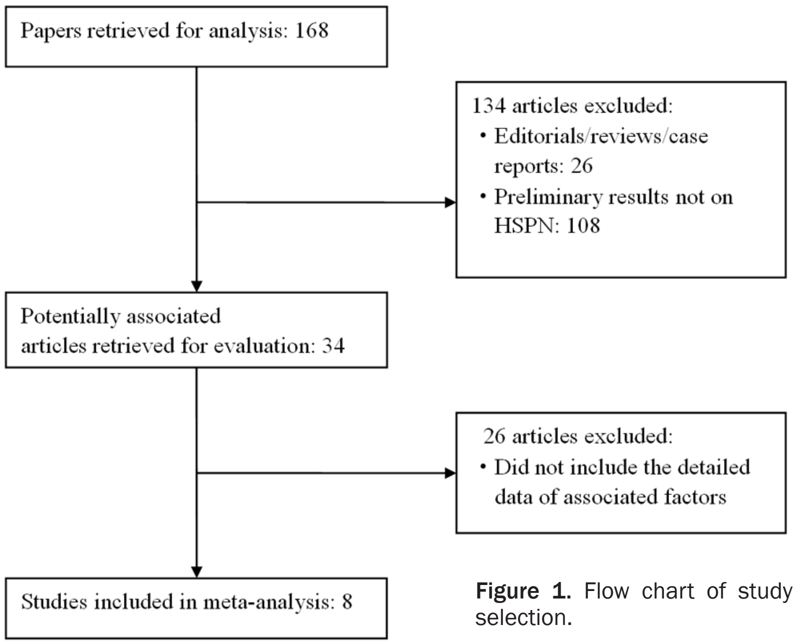

Figure 1. Flow chart of study selection.

parison between HSP and HSPN with the aims as follows: 1) investigate the risk factors for the onset of renal damage of HSP; 2) identify the risk factors relevant to the severity of renal damage of HSPN according to the International Study Kidney Disease in Children (ISKDC) classification.

Materials and methods

Search strategy

We attempted to search the papers that reported the associated factors (age, SBP, WBC, PLT, ALB, IgA, IgG, IgM, C3, Hb, BUN and Scr) both in HSP and HSPN patients from January 1990 to February 2015 using PubMed, Embase and Cochrane databases. The used search terms were as follows: 1) age, SBP, WBC, PLT, ALB, IgA, IgG, IgM, C3, Hb, BUN, Scr; 2) HSP, HSPN, purpura, nephritis; 3) risk, incidence; and 4) standard mean difference (SMD) and the corresponding 95% confidence interval (CI) (or data to calculate them) for the potential risk factors were reported. We also reviewed the references lists of extracted publications. If the same participants were included in more than one study, we enrolled the study with the most complete analysis.

Data collection and quality assessment

We extracted the data of study characteristics as follows: first author's surname; publication year; ethnicity; age; number of HSP and HSPN; the levels of SBP, WBC, PLT, ALB, IgA, IgG, IgM, C3, Hb, BUN and Scr. Two authors conducted the literature search and data collection with any disagreement resolved by discussion. Additionary, we assessed the quality of the enrolled study using Newcastle-Ottawa Quality Assessment Scale, including participants' selection, exposure and comparability. A study can be given a maximum of one score for each numbered item within the selection and exposure categories. A maximum of two socres can be given for comparability.

Statistical analysis

Standard mean deviation (SMD) was used to determine the differences of age, SBP, WBC, PLT, ALB, IgA, IgG, IgM, C3, Hb, BUN and Scr across studies between HSP and HSPN patients. Heterogeneity of SMDs across studies was tested using the Q statistic at the significance level of $P < 0.05$. The pooled SMDs were calculated by using either fixed-effects models or, in the presence of heterogeneity, random-effects models. The pooled analyses were conducted by using STATA version 12.0 (Stata Corp, College Station, TX). A P value < 0.05 was considered statistically significant.

Results

According to searching criteria, eight studies [13-20] were enrolled (**Figure 1**).

The number of awarded scores of included studies ranged from 5 to 8 (low quality: 1-3, median quality: 4-6, high quality: 7-9). Five studies [14-18] were awarded for five scores, two [19, 20] for six scores, and one [13] for seven scores.

The characteristics of eight previous publications are shown in **Table 1**. A total of 700 HSP and 522 HSPN patients from eight previous publications were enrolled for the comparisons between HSP and HSPN (**Table 1**). Age, SBP, C3, Hb, and BUN were significantly lower in HSP

Table 1. Characteristics of previous studies regarding comparison between HSP and HSPN

Study	Ethnicity	N	Age (year)	SBP (mmHg)	WBC ($\times 10^9$/L)	PLT ($\times 10^9$/L)	ALB (g/L)	IgA (g/L)	IgG (g/L)	IgM (g/L)	C3 (g/L)	Hb (g/L)	BUN (mmol/L)	Scr (mmol/L)
Kawasaki et al 2005	Asian	12/20	7.7 (1.6)/ 8.1 (2.7)	-	8.8 (3.8)/ 10.2 (4.6)/uL	-	-	-	—	—	—	—	—	—
Lau et al 2007	Caucasian	6/26	7.9 (4.6)/ 9.8 (4.2)	-	-	-	-	-	—	—	—	—	—	—
He et al 2012	Asian	269/61	7.16 (2.55)/ 8.36 (2.75)	-	-	-	-	-	—	—	—	—	—	—
Nickavar et al 2012	Asian	64/41	63.7 (31.7)/ 87.4 (30.9)	-	-	-	-	-	—	—	—	—	—	—
Ru et al 2013	Asian	31/28	8.1 (3.0)/ 8.7 (2.9)	-	10.6 (6.7)/ 9.6 (5.2)	284 (114)/ 298 (114)	-	2.5 (1.2)/ 2.4 (1.1)	9.3 (3.3)/ 9.1 (3.3)	1.4 (0.6)/ 1.6 (0.7)	1.03 (0.24)/ 1.33 (0.73)	119 (22)/ 129 (13)	—	—
Kimura et al 2013	Asian	16/42	48.06 (2.28)/ 52.90 (19.45)	-	-	-	-	4.1 (1.6)/ 4.4 (2.1)	—	—	—	—	—	—
Mao et al 2014	Asian	268/ 267	6.38 (2.53)/ 7.48 (2.79)	100.9 (10.1)/ 102.8 (10.6)	11.8 (4.98)/ 12.3 (5.12)	334 (108)/ 340 (118)	37 (4.5)/ 35.8 (6.1)	2.11 (0.73)/ 2.16 (0.81)	11 (6)/ 10.2 (3.4)	1.24 (0.91)/ 1.27 (1.00)	—	—	—	—
Ge et al 2014	Asian	34/37	6.78 (2.73)/ 6.97 (2.17)	-	-	-	-	-	—	—	—	—	3.09 (0.88)/ 3.61 (1.25)	26.68 (11.75)/ 28.43 (12.24)

HSP: Henoch-Schonlein purpura, HSPN: Henoch-Schonlein purpura nephritis, SBP: systolic blood pressure, WBC: white blood cell, PLT: platelet, ALB: albumin, Hb: hemoglobulin, BUN: blood urea nitrogen, Scr: serum creatinine. HSP/HSPN.

Table 2. The differences of various indexes between HSP and HSPN

Index	Studies	Q test	Model selected	SMD (95% CI)	*P*-value
		P-value			
Age	8	0.527	Fixed	-0.407 (-0.529-0.285)	$< 10^{-4}$
SBP	1	-	Fixed	-0184 (-0.353-0.014)	0.034
WBC	3	0.504	Fixed	-0085 (-0.242-0.072)	0.290
PLT	2	0.800	Fixed	-0.060 (-0.221-0.101)	0.465
ALB	1	-	Fixed	0.224 (0.054-0.394)	0.010
IgA	3	0.813	Fixed	-0.057 (-0.212-0.098)	0.469
IgG	2	0.707	Fixed	0.154 (-0.007-0.315)	0.061
IgM	2	0.317	Fixed	-0.059 (-0.221-0.103)	0.477
C3	1	-	Fixed	-0.564 (-1.086--0.043)	0.034
Hb	1	-	Fixed	-0.547 (-1.067--0.026)	0.040
BUN	1	-	Fixed	-0.478 (-0.950--0.005)	0.048
Scr	1	-	Fixed	-0.146 (-0.612-0.321)	0.540

HSP: Henoch-Schonlein purpura, HSPN: Henoch-Schonlein purpura nephritis.

compared with those in HSPN ($P \leq 10^{-4}$, 0.034, 0.034, 0.040, and 0.048, respectively, **Table 2**; **Figure 2**). ALB was markedly higher in HSP in comparison to that in HSPN ($P = 0.010$, **Table 2**). No significant differences of WBC, PLT, IgA, IgG, IgM and Scr between HSP and HSPN were noted (**Table 2**).

Discussion

Increasing attention has been paid to the risk factors of renal damage of HSP. To our knowledge, this is the first meta-analysis investigating the risk factors for renal damage of HSP and we firstly pooled the previous publications regarding the comparisons between HSP and HSPN. Our study indicated that age, SBP, DBP, WBC, Hb, PLT, hematuria, BUN, Scr, Chol, C3, C4, IgA, IgG and IgM have no impact on the severity of renal damage of HSP. Elevated Age, SBP, C3, Hb, and BUN and decreased ALB are risk factors for renal damage onset in HSP patients. WBC, PLT, IgA, IgG, IgM and Scr have no influence on the onset of renal damage of HSP. Our findings suggest that monitoring the common biochemical indexes may be helpful for the prevention and evaluation of renal damage of HSP.

Several mechanisms may account for our findings. First, HSP is likely to occur in children, renal damage often occur 4 to 6 weeks, or even longer after HSP onset [21], which may explain that HSP cases are markedly younger than HSPN. On the other hand, children do not usually present with kidney injury-associated diseases, such as diabetes and hypertension [22], which may also account for that lower age of children present with less kidney injury. Hypertension may induce renal injury [23], children may have not persistent higher blood pressure compared with adults, which account for that HSP had significantly lower SBP compared with HSPN. Second, renal damage causes the loss of albumin [24], the albuminuria may exacerbate the kidney injury, compared with HSP, HSPN is likely to present with hematuria, which may lead to decreased Hb. Meanwhile, severe HSPN often present with heavy proteinuria, HSPN patients usually present with lower blood volume due to the loss of albumin compared with HSP, which may induce the increase of BUN. HSPN cases are likely to have more glomerular deposition of IgA and C3 [25], the complement activation occurs in HSPN, which may explain the fact that HSPN cases had markedly higher C3 compared with HSP. Finally, the negative differences of WBC, PLT, IgA, IgG, and IgM between HSP and HSPN indicated that the renal damage of HSPN may not be correlated with infection, coagulable state, and immunologic state. We speculated that unlike nephrotic syndrome/IgA nephropathy, HSPN patients do not usually have specific history of infection and more synthesis of Chol [26]. Unlike systemic lupus erythematosus (SLE), the immune dysfunction of HSPN is mild, which may account for the null differences of these indexes. Nevertheless, our findings have great implications that monitoring certain indexes may be helpful for the evaluation of the renal damage of HSP, on the other hand, the positive indexes we found were more simple, feasible and relatively non-invasive.

In the past, several studies were performed to investigate the factors relevant to renal damage of HSP. Chang et al [27] reported that aberrant activation of Toll-like receptor 4 (TLR4) levels exhibited a positive correlation with urinary protein excretion. Fuentes et al [28] reported that urinary MCP-1/creatinine levels were ele-

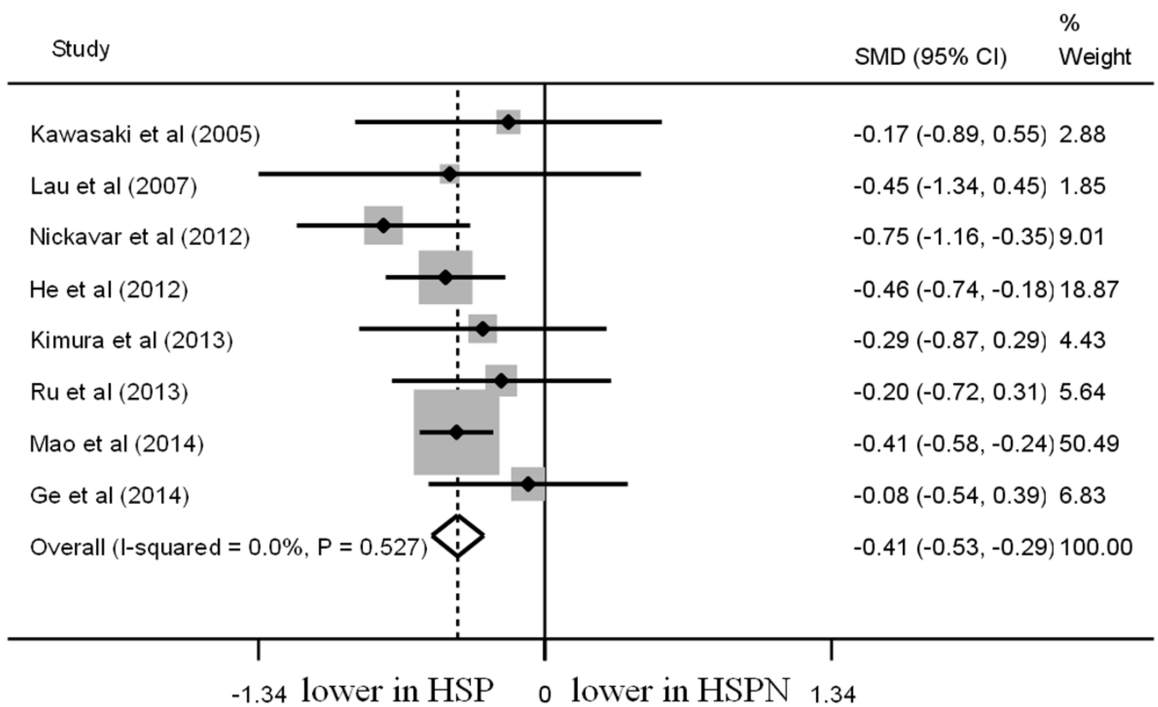

Figure 2. The differences of age between HSP and HSPN.

vated in the early stages of severe HSPN. Ru et al [29] reported that HSPN patients with proteinuria had significantly higher serum levels of IGF-1 and IGFBP-3 than those without proteinuria. Ge et al [14] reported that plasma PTX3 concentration was positively correlated with CRP, MALB, and 24-h urinary protein in HSPN. Zhang et al [30] reported that the α-SMA levels of HSPN group were positively correlated with the BUN and Scr levels. All these reports supported the notion that the confirmed indicators of HSPN were almost all closely associated with certain biochemical indexes of HSP, which further support our findings.

Our study had obvious strengths that we pooled the previous publications together to yield robust results than a single investigation. Several limitations should also be considered in our study. First, the retrospective design of some enrolled studies might lead to recall bias, which may affect the reliability of the extracted data. The participants from eight previous publications were mainly Caucasians; other populations should be investigated in the future. Second, the limited number of study populations decreased the statistical power. Hence, a larger number of studies should be conducted in the future.

In conclusion, our investigation suggests that elevated age, SBP, C3, Hb, and BUN and decreased ALB are risk factors for renal damage onset in HSP patients. However, larger number of studies should be performed to validate our findings.

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Disclosure of conflict of interest

None.

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