



# The efficacy and safety of immunosuppressive agents plus steroids compared with steroids alone in the treatment of Henoch–Schönlein purpura nephritis: A meta-analysis

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## Abstract

**Background** Henoch–Schönlein purpura nephritis (HSPN) is the most severe symptom of Henoch–Schönlein purpura. The role of immunosuppressive agents combined with steroids is controversial in treating HSPN. Our meta-analysis was performed to assess the efficacy and safety of the combined therapy in the treatment of HSPN compared with steroids alone.

**Methods** Cochrane Library, Pubmed, Embase, and Web of Science were searched and Newcastle–Ottawa Scale was used to assess the quality of the literatures. Odds ratios (OR) and standard mean difference (SMD) with a 95% confidence interval (CI) were used for dichotomous and continuous variables. A random-effect model or fixed-effect analysis was applied according to heterogeneity.

**Results** A total of 9 articles were selected in our study. HSPN patients treated with combined therapy demonstrated a significant increase in complete remission rates (OR = 1.95; 95% CI 1.17–3.23,  $P=0.010$ ) and total remission rates (OR = 2.30 95% CI 1.33–3.98,  $P=0.003$ ) when compared with steroids alone. Children seemed to benefit more from combined treatment (OR = 2.45; CI 1.20–5.02,  $P=0.014$ ) than adults (OR = 1.56; CI 0.76–3.20,  $P=0.225$ ). Additionally, immunosuppressants plus steroids had an advantage on decreasing proteinuria (SMD = 0.28; CI 0.05–0.52,  $P=0.019$ ) and increasing the level of serum albumin (SMD = 0.98; CI 0.35–1.60,  $P=0.002$ ). However, significant differences were not found in the estimated glomerular filtration rate (eGFR) and rates of side-effects.

**Conclusion** Administration of immunosuppressive agents combined with steroids may be a superior alternative for HSPN. Nevertheless, long-term, high-quality, large-sample, and multicenter RCTs are required to make the results more convincing.

**Keywords** Henoch–Schönlein purpura nephritis · HSPN · Immunosuppressive agents · Steroids · Meta-analysis

## Introduction

Henoch–Schönlein purpura (HSP) is one of the most common forms of systematic vasculitis, with an incidence about 10 cases per 100,000 every year [1]. People of any age can

be affected by HSP, while the majority of those are under 10 years old [2]. Purpuric rashes are the most typical manifestation, but HSP can also impair the joints, gut, and kidney to different extent. Henoch–Schönlein purpura nephritis (HSPN) is a relatively serious complication, characterized by microscopic or gross hematuria with or without proteinuria [3]. It is reported that approximately 30% of them have nephrotic-range proteinuria and HSPN, especially with nephrotic proteinuria, can result in end-stage renal disease (ESRD) or death despite that HSP is generally thought to be a self-limiting disorder with a favorable prognosis [4, 5].

Optimum treatment strategies are of great significance for patients with HSPN to achieve clinical recovery or remission. Steroids have been the first-line therapeutic regimen for many kinds of glomerulonephritis over years. Immunosuppressive agents are also commonly used drugs for kidney disease in clinical practice. However, the efficacy and

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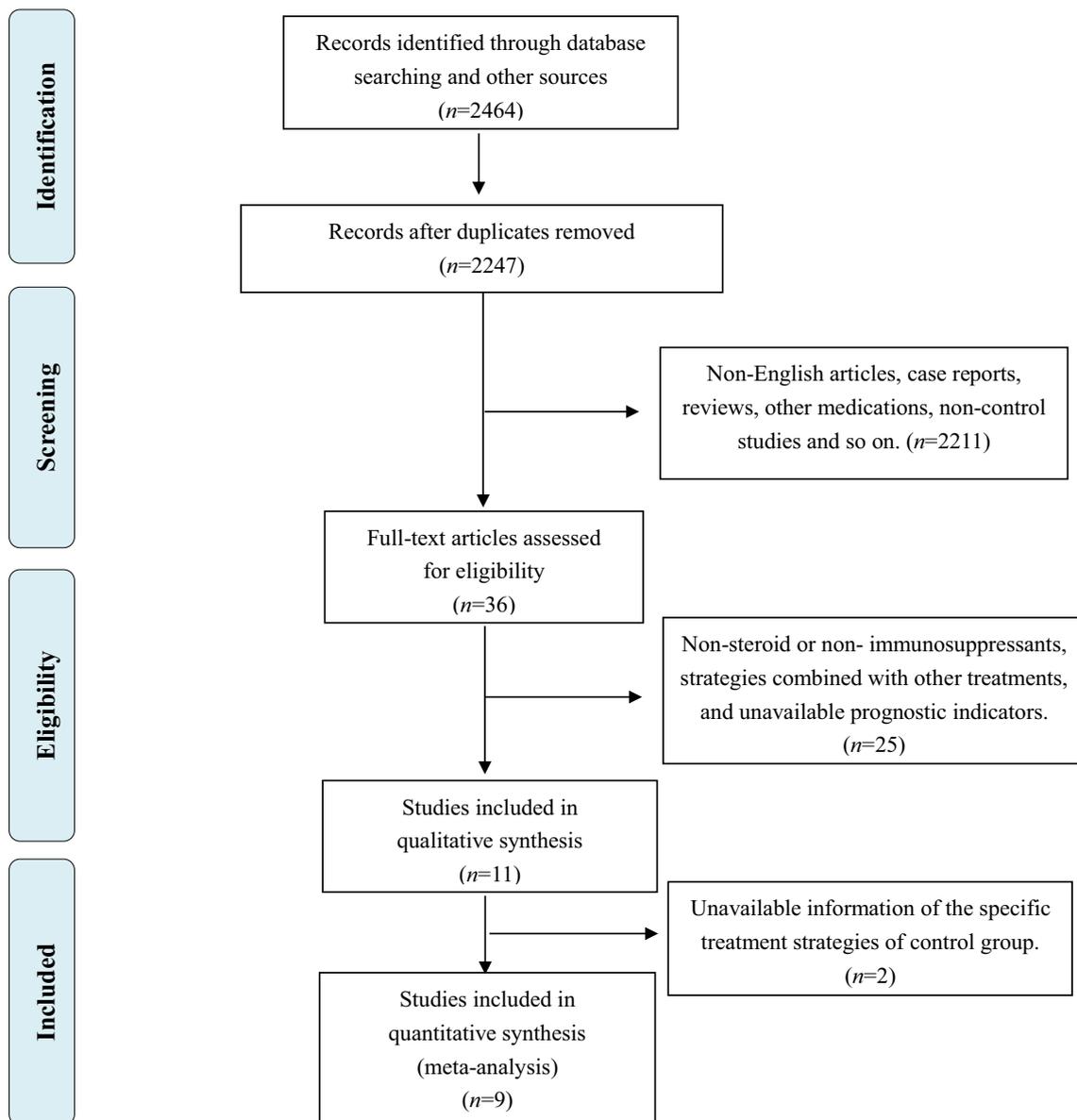
safety of the therapy of steroids and immunosuppressants in treating HSPN are still controversial. The treatment of HSPN guided by KDIGO is much more like that of immunoglobulin A nephropathy (IgAN), and immunosuppressants are not recommended due to the little evidence of the therapy of HSPN [6]. Although some scholars consider that HSPN is a systemic form of IgAN, both of which have the similar clinicopathologic features, there are still many differences between both diseases [7, 8]. A viable and effective therapy with compelling evidence should be found to treat the HSPN. Therefore, this meta-analysis is carried out to evaluate the benefits and safety of the therapy of steroids

combined with immunosuppressive agents, compared with steroids alone.

## Materials and methods

### Search strategy

Two independent investigators integrated commonly used databases by using the well-designed search terms. The databases which were searched for eligible articles included the Cochrane Library (February 2018), Pubmed (1966 to February 2018), the Embase databases via Ovid (1974 to March



**Fig. 1** Flowchart illustrating the selection of studies

**Table 1** Characteristics of the selected studies

Authors	Year	Study type	Nationality	T	C	Number enrolled		Age		Follow-up	
						T (M/F)	C (M/F)	T	C	T	C
Kawasaki [12]	2004	R	Japan	S + CTX	S	17 (8/9)	20 (9/11)	7.1 ± 3.1	8.0 ± 2.8	24 m	24 m
Zhang [13]	2014	R	China	S + LET	S	38 (24/14)	27 (15/12)	48.2 ± 12.7	51.2 ± 14.7	48 m	47.2 m
Shin [14]	2005	R	Korea	S + AZA	S	10 (8/2)	10 (7/3)	9.6	9.0	4.4 y	5.5 y
Devidayal [15]	2002	R	India	S + AZA	S	9 (6/3)	2 (NA)	8.05	10.25	4.7 y	4.7 y
Lu [16]	2017	R	China	S + MMF	S	41 (23/18)	20 (9/11)	7.61 ± 2.87	7.79 ± 2.88	23.29 m	27.1 m
Ren [17]	2012	R	China	S + MMF	S	27 (13/14)	26 (13/13)	28.04 ± 14.09	25.92 ± 14.28	28.2 m	28.8 m
Han [18]	2015	R	China	S + MMF	S	33 (13/20)	31 (14/17)	31 ± 15	29 ± 16	28 m	29 m
Mizerska-Wasiak [19]	2016	R	Poland	S + AZA or CTX	S	23 (NA)	9 (NA)	9.6 ± 3.3	9.8 ± 4.1	> 2 y	> 2 y
Pillebout [20]	2010	P	French	S + CTX	S	25 (17/8)	29 (19/12)	52.8 ± 18.5	60.7 ± 11.0	59.8 m	60.9 m

A total of 9 articles were included in our study  
 T treatment group, C control group, R retrospective study, P prospective study, S steroids, CTX cyclophosphamide, LET leflunomide, AZA azathioprine, MMF mycophenolate mofetil, NA not available, m months, y years

2018), and Web of Science (1900 to March 2018). We used Henoch–Schönlein purpura with its all synonyms as terms instead of Henoch–Schönlein purpura nephritis. Moreover, mycophenolic acid, cyclosporine, cyclophosphamide, azathioprine, tacrolimus, leflunomide, and immunosuppressive agents were used as the mesh terms to investigate the articles we required, as well as their all entry terms (Table SS1). And the spectrum of our search was also included in “related article” and bibliographies for additional references.

**Inclusion and exclusion criteria**

The inclusion criteria and exclusion criteria were pre-designed as to select the requisite articles.

The inclusion criteria were as follows. (a) Retrospective study or randomized controlled trial (RCT) about the treatment of HSPN which was proven by renal biopsy. (b) At least two comparison groups (steroid + immunosuppressant versus steroid group). (c) The language is limited to English. (d) The data of curative effect and safety in treating HSPN could be obtained in some way or other.

Following are the exclusion criteria. (a) Other non-English articles. (b) Animal experiments. (c) Case reports. (d) Editorials or review papers. (e) The data reflecting the efficacy and safety was unavailable. (f) Other immunosuppressants like traditional Chinese medicine with uncertain components and additional function. (g) Other diseases like HSP and IgAN whose specific data could not be divided.

**Study selection and data extraction**

Two independent investigators evaluated all the studies which were included in the present meta-analysis, based on inclusive and exclusive criteria through titles and abstracts; then, the full texts of all relevant studies were analyzed. The discrepancies were pointed out to resort to the third one.

After that, the investigators independently extracted data by using the same Excel table designed previously. The parts expressed in tabular form were the name of the author, publication year, study type, nationality, demographic characteristics, numbers of the patients enrolled in different groups, therapeutic schedules, duration of follow-up, pathology, side-effects, remission rates, and data of laboratory examinations. The consensus was reached by consulting the third investigator when disagreements happened. If the data of the relevant articles were lacking, the corresponding author was contacted for the information by sending the e-mail.

**Outcome measurements**

To evaluate the efficacy and safety of adding immunosuppressive agents to steroids, the complete and total remission

**Table 2** Baseline laboratory indicators and NOS scores of the selected studies

Authors	Proteinuria		eGFR (ml/min/1.73 m <sup>2</sup> )		Serum albumin (g/L)		NOS score	
	Units	T	C	T	C	T		C
Kawasaki	mg/h/m <sup>2</sup>	181 ± 85	154 ± 73	NA		27 ± 6	29 ± 4	8
Zhang	g/24 h (25–75%)	7.8 ± 2 (6.3–9.0)	8 ± 2.4 (5.5–8.7)	58.2 ± 17.4	61.2 ± 17.7	NA		8
Shin	g/m <sup>2</sup> /day	5.0 ± 4.5	1.4 ± 0.5	NA		NA		7
Devidayal	g/m <sup>2</sup> /day	4.2 ± 2.5	NA	NA		NA		6
Lu	mg/m <sup>2</sup>	96.69 ± 50.12	82.15 ± 29.36	NA		NA		8
Ren	g/24 h	3.88 ± 2.04	3.72 ± 2.22	124.4 ± 45.1	140.2 ± 46.2	NA		7
Han	g/24 h	2.1 ± 0.9	1.9 ± 1.0	117.4 ± 32.7	109 ± 36.3	38.5 ± 5.4	39.9 ± 5.7	7
Mizerska-Wasiak	mg/kg/dL (min–max)	87.0 (6.2–628.0)	24.2 (7.2–179)	140 ± 28	155 ± 45	34 ± 0.7	39 ± 0.8	6
Pillebout	g/24 h (min–max)	3.6 (0–12)	3.2 (0–21)	76 (9–132)	60 (10–125)	NA		–

NOS Newcastle–Ottawa Scale, which considered the selection, comparability, and outcome of the retrospective study. Therefore, all studies got a score except the prospective study

NA not available

**Table 3** Definitions of clinical remission in the selected studies

Authors	Definition		
	Complete remission (CR)	Partial remission (PR)	Total remission (TR)
Kawasaki	Normal physical examination, urine, and renal function	Minor urinary abnormalities <sup>a</sup>	CR + PR
Zhang	Proteinuria < 0.3 g/24 h, without an obvious decrease in the eGFR level	–	CR
Shin	Normal physical examination, urine, and renal function	Minor urinary abnormalities <sup>b</sup>	CR + PR
Devidayal	Normal physical examination, urine, and renal function	Minor urinary abnormalities <sup>b</sup>	CR + PR
Lu	Normal physical examination, urine, and renal function	Minor urinary abnormalities <sup>a</sup>	CR + PR
Ren	Proteinuria < 0.2 g/day, without decrease in eGFR or hematuria	–	CR
Han	Proteinuria ≤ 0.3 g/24 h, without an obvious decrease in the eGFR level	–	CR
Mizerska-Wasiak	With no proteinuria	–	CR
Pillebout	–	Proteinuria < 1 g/day	PR

<sup>a</sup>Minor urinary abnormalities: proteinuria < 20 mg/m<sup>2</sup>/h with or without microscopic-recurrent macroscopic hematuria

<sup>b</sup>Minor urinary abnormalities: normal on physical examination with microscopic hematuria or proteinuria less than 40 mg/m<sup>2</sup>/h

rates, decreasing level of proteinuria, increasing level of serum albumin and eGFR, and rates of adverse effects were taken into account. Different studies had their own definition of complete and partial remission, but all of them used the reduction of urinary protein as the indicator. Synthesized each kind of situation, the definition of complete remission was proteinuria ≤ 0.3 g/day, without decrease in eGFR, and the partial remission was defined as the minor urinary abnormalities with proteinuria < 40 mg/m<sup>2</sup>/h.

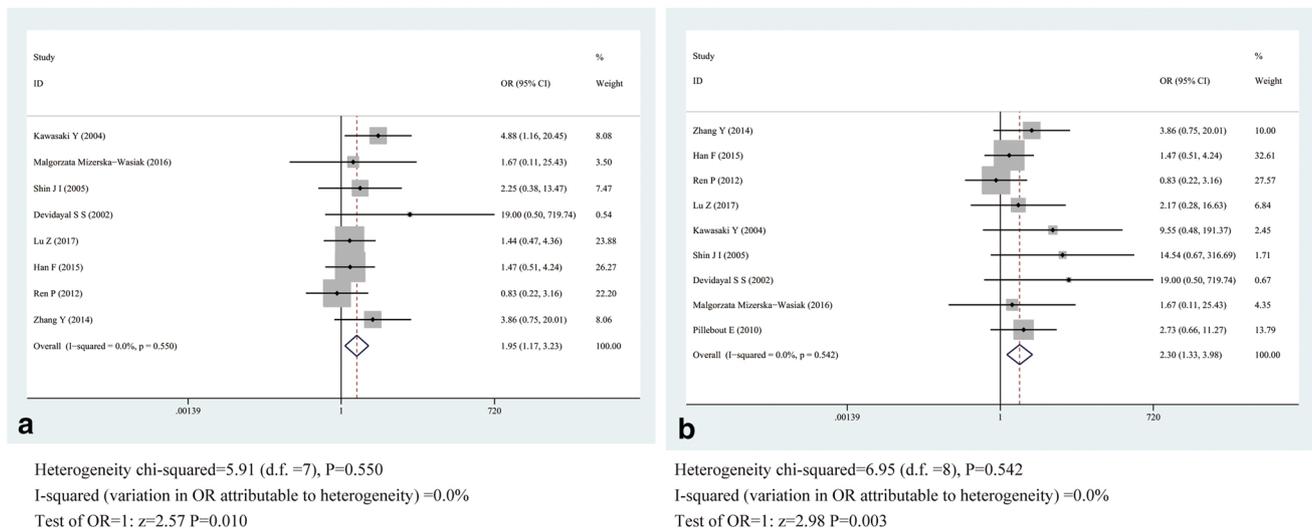
### Assessments of methodological quality and statistical analysis

Since the selected articles were mostly retrospective after literature screening, the Newcastle–Ottawa Scale, which considered the selection, comparability, and outcome of the

retrospective study, was used to assess the quality of studies that was scored from 0 to 9 by two investigators.

Odds ratios (OR) with its 95% confidence interval (CI) were analyzed for dichotomous outcomes, while the standard mean difference (SMD) was chosen for continuous variables, described with a 95% CI. However, in some literature studies, the median with quartiles or ranges was reported and standard deviation (SD) of change was not given directly. The formulas we used to calculate the indirect data are illustrated in Fig. S51, which were guided by the Cochrane handbook for systematic review of interventions [9]. STATA version 12.0 (STATA Corporation, College Station, TX) was used to conduct meta-analysis. We applied a random-effect model or a fixed-effect analysis depending on  $I^2$  which was to measure the heterogeneity. Fixed-effect was used when  $I^2 \leq 50\%$ ; otherwise, random-effect model was applied.

Because the number of included studies was less than 10, there was no need to assess the publication bias.



**Fig. 2** Meta-analysis on the remission rates of the immunosuppressive agents plus steroids compared with steroids alone. Comparison of complete remission rates (a) and total remission rates (b)

## Results

### Study selection

A total of 2464 references were collected using the established search strategy from various databases. After the strict screening of articles in accordance with uniform criteria by their title and abstract, 2428 references were excluded for several reasons (217 of which were duplications and the rest of which were not reaching the standards). Then, we assessed the full-text article to confirm whether they were eligible. Overall, 36 references were reviewed while 11 references remained. The reason for exclusion included the treatment strategies without steroids or immunosuppressants, strategies combined with other treatments which could affect the result, unavailable prognostic indicators reflecting the efficacy and safety of HSPN, and other exclusion criteria which were shown above. Notably, 2 articles of the remaining ones investigated the curative effect between immunosuppressant therapy and the mixed protocols, where we were not able to get the specific treatment strategies because the control group was treated with or without steroids and it could not be divided. Because the detailed information could not be obtained through email inquiry, these 2 articles were excluded [10, 11]. Ultimately, 9 references were included in quantitative synthesis. The flow-chart presenting our strategies is shown in Fig. 1.

### Characteristics of studies

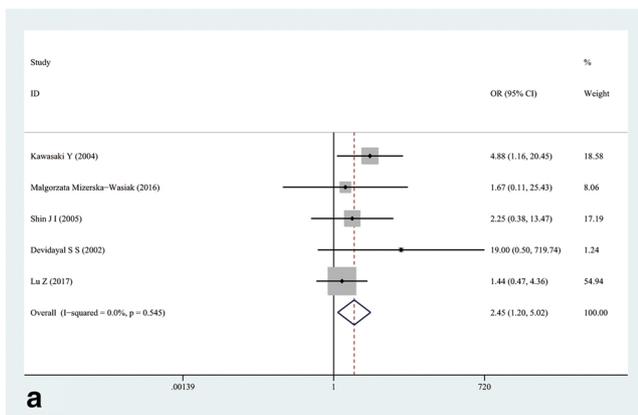
Tables 1 and 2 reveal the characteristics of the selected articles. There were 9 articles comparing the effect and safety

between steroids combined with immunosuppressants and steroids alone. Patients in experiment group were treated with immunosuppressants combined with steroid and the control group received steroid alone. The immunosuppressants for HSPN illustrated in the studies included cyclophosphamide, azathioprine, mycophenolate mofetil, and leflunomide. It was well to be reminded that all studies were retrospective except one, a prospective and open-label trial [20]. Therefore, all retrospective studies got a mark according to the Newcastle–Ottawa Scale, presented in Table 2 and Table SS2. All scores were over 6, suggesting that their outcomes were convictive.

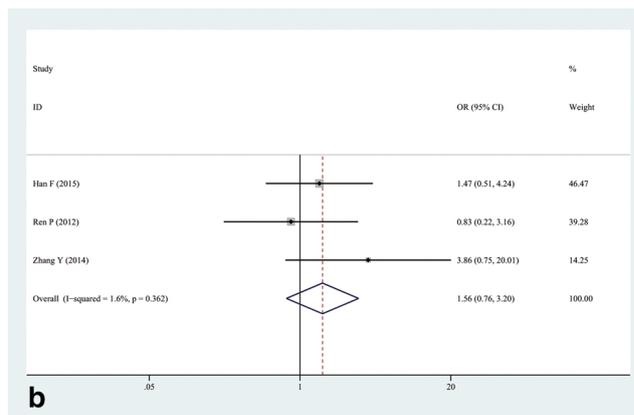
The definitions of clinical remission in various papers are shown in Table 3 and the total remission included complete remission and partial remission. The definition of complete remission which was frequently used in respective studies was normal physical examination, urine, and renal function. The partial remission was defined as the minor urinary abnormalities with proteinuria < 40 mg/m<sup>2</sup>/h.

### Effect of combine therapy on remission rates

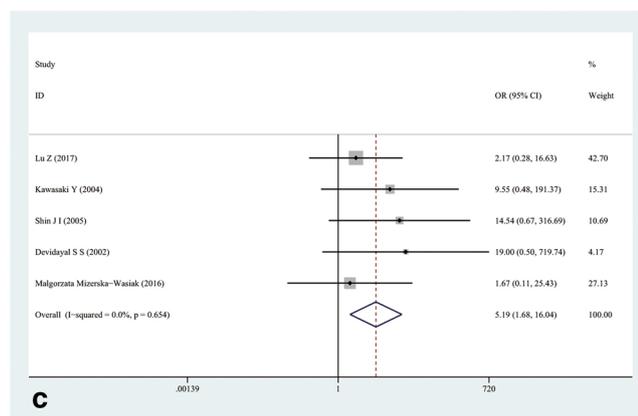
As presented in Fig. 2, patients treated with immunosuppressants combined with steroids demonstrated a significant increase in complete remission rates (Fig. 2a OR = 1.95; 95% CI 1.17–3.23,  $P=0.010$ ) and total remission rates (Fig. 2b OR = 2.30 95% CI 1.33–3.98,  $P=0.003$ ) when compared with steroids alone. Taking complete remission as an evaluation index, children seemed to benefit more from combined therapy (Fig. 3a OR = 2.45; CI 1.20–5.02,  $P=0.014$ ) than adults (Fig. 3b OR = 1.56; CI 0.76–3.20,  $P=0.225$ ). But there was a slight trend that adult patients had more



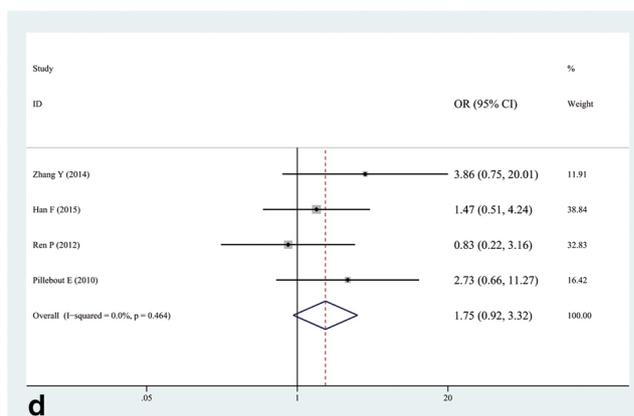
Heterogeneity chi-squared=3.08 (d.f. = 4), P = 0.545  
 I-squared (variation in OR attributable to heterogeneity) =0.0%  
 Test of OR=1: z=2.45 P= 0.014



Heterogeneity chi-squared =2.03 (d.f. = 1) p = 0.362  
 I-squared (variation in OR attributable to heterogeneity) =1.6%  
 Test of OR=1: z=1.21 P= 0.225



Heterogeneity chi-squared =2.45 (d.f. = 4) p = 0.654  
 I-squared (variation in OR attributable to heterogeneity) =0.0%  
 Test of OR=1: z=2.86 P= 0.004



Heterogeneity chi-squared =2.56 (d.f. = 3) p = 0.464  
 I-squared (variation in OR attributable to heterogeneity) =0.0%  
 Test of OR=1: z=1.72 P= 0.085

**Fig. 3** Meta-analysis on the remission rates of different age patients. Comparison of complete remission rates in children (a), complete remission rates in adults (b), total remission rates in children (c), and total remission rates in adults (d)

total remission rates (Fig. 3d OR = 1.75; CI 0.92–3.32, P = 0.085). Additionally, subgroup analysis revealed that azathioprine added to steroids was a more effective treatment (Fig. 4a OR = 6.67; 95% CI 1.33–33.36, P = 0.021) in children while mycophenolate mofetil combined with steroids was as efficient as steroids alone (Fig. 4b OR = 1.28; 95% CI 0.59–2.75, P = 0.530). Notably, the rest of the immunosuppressive agents were not analyzed for lack of enough studies.

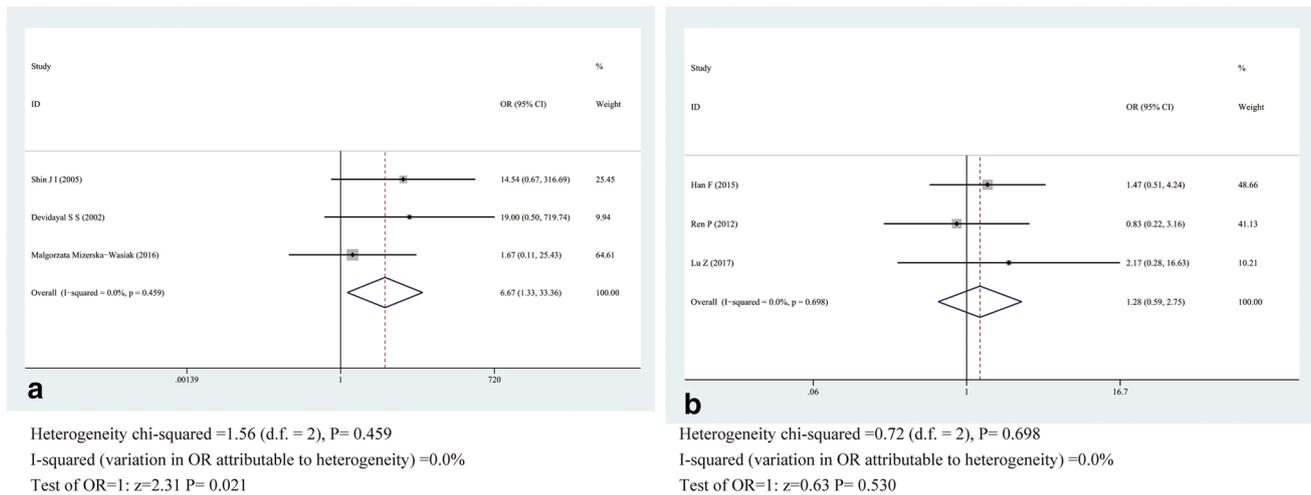
**Effect of combined therapy on proteinuria, serum albumin, and eGFR level**

Our study also found that immunosuppressants plus steroids had an advantage on decreasing proteinuria (Fig. 5a SMD = 0.28; CI 0.05–0.52, P = 0.019) and increasing the level of serum albumin (Fig. 5b SMD = 0.98; CI 0.35–1.60, P = 0.002). However, there was no evidence to prove that

immunosuppressants could increase eGFR more effectively (Fig. 5c SMD = 0.25; CI -0.26–0.75, P = 0.338) but patients seemed to have a slightly higher level of eGFR after the combined therapy (Fig. 5d SMD = 0.21; CI -0.05–0.48, P = 0.110).

**Adverse effects of the combine therapy**

Seven studies had reported the side-effects of combined therapy and steroid alone, one of which demonstrated that patients of both groups had no therapy-related complications. No significance was presented in the rates of infection (Fig. 6a OR = 0.69; CI 0.37–1.26, P = 0.225), leukopenia (Fig. 6b OR = 1.45; CI 0.34–6.28, P = 0.616), and abnormal liver function (Fig. 6c OR = 1.50; CI 0.46–4.86, P = 0.500). Nevertheless, there was a tendency that the



**Fig. 4** Total remission rates in all studies comparing various immunosuppressants plus steroids and steroids alone, including the treatment of azathioprine plus steroids (**a**) and mycophenolate mofetil plus steroids (**b**)

number of patients with the side-effect of hypertension was less (Fig. 6d OR = 0.30; CI 0.08–1.15,  $P = 0.078$ ).

### Subgroup analysis of the experimental method

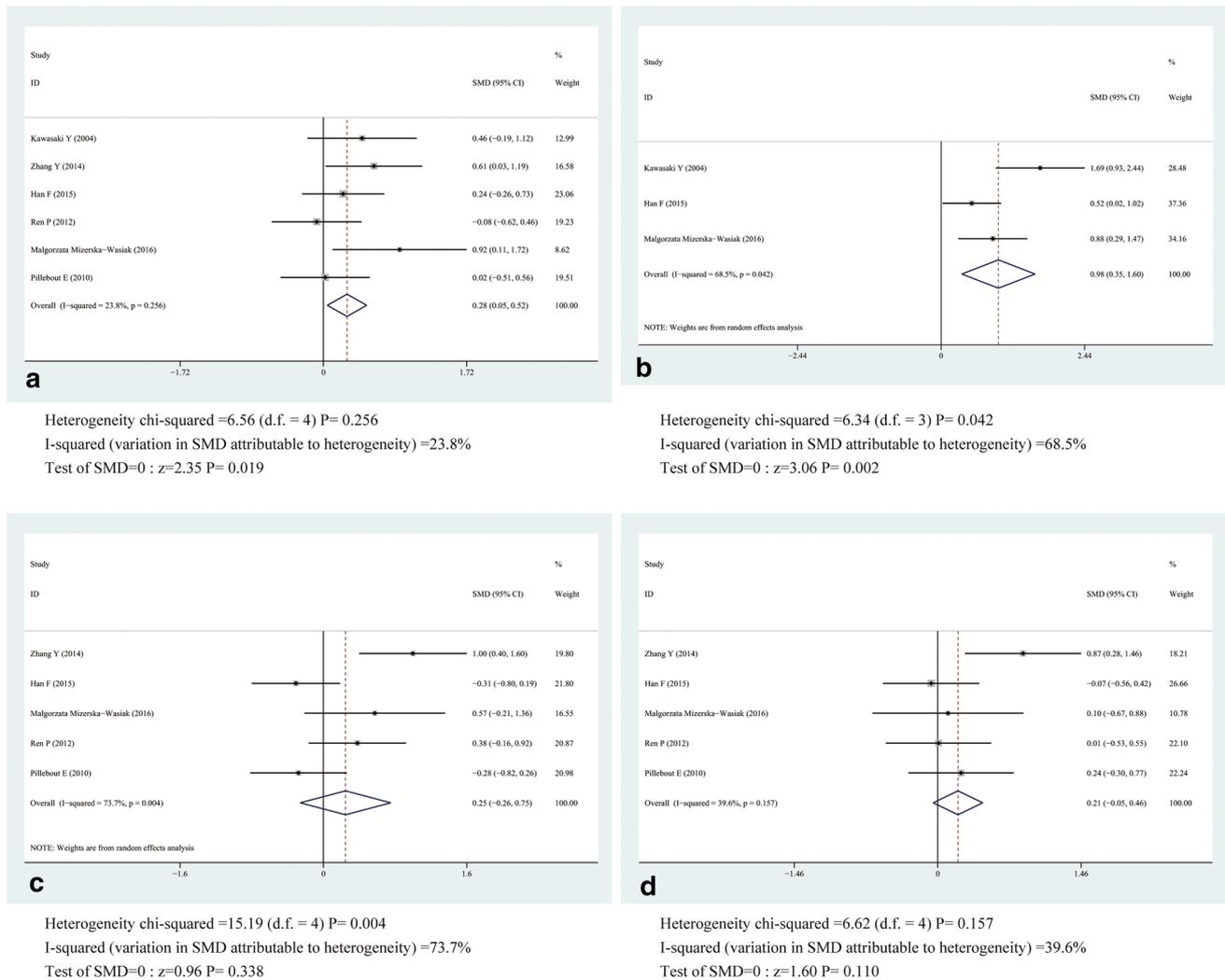
A total of 8 retrospective studies and 1 prospective study were included in our meta-analysis. Considering that different experimental methods might lead to heterogeneity, subgroup analysis was conducted to eliminate this effect. Data of all retrospective studies were resynthesized, but the results, which are presented in Fig. SS2, did not change much.

### Discussion

HSP is one of the most common vasculitis, with a relatively favorable prognosis. Involving in the gut, lung or kidney, this disease can also be life-threatening [1]. HSPN is the relatively severe complication of HSP. Although the majority of HSPN patients have mild symptoms, some patients can get even worse, which will progress to nephrotic syndrome and/or ESRD [21]. About 5–15% of pediatric patients with HSPN develop chronic renal failure and approximately 30% in adults [22]. Although some researches have reported that early aggressive immunosuppressive treatment is benefit to patients with HSPN, immunosuppressive agents are still not recommended in guidelines due to the lack of reliable evidence [6]. Since a deal of researches have demonstrated the role of immunosuppressive agents combined with steroids, this meta-analysis is performed to clarify the efficacy and safety of immunosuppressive agents combined with steroids.

Our meta-analysis demonstrated that the curative effect of immunosuppressive agents combined with steroids was superior to that of steroids alone in treating HSPN. There were more patients who were treated with immunosuppressants plus steroids achieving complete remission, compared with steroids (OR = 1.95; 95% CI 1.17–3.23,  $P = 0.010$ ), especially in pediatric patients (OR = 2.45; CI 1.20–5.02,  $P = 0.014$ ), which indicated that immunosuppressive agents combined with steroids were a more effective way to treat the HSPN patients than steroids alone. However, the differences in complete remission rates of adult patients made no statistical significance (OR = 1.56; CI 0.76–3.20,  $P = 0.225$ ) but there was a slight trend on increasing total remission rates of adults (OR = 1.75; CI 0.92–3.32,  $P = 0.085$ ). It is well accepted that the age plays an important part in determining the manifestation and severity for HSP patients, and adult patients usually have a relatively poor prognosis [23]. The research carried out recently has demonstrated that patients with HSPN in different age have various clinicopathological features, and the chronic index of renal pathology was higher in adults, suggesting that the chronicity is more severe in adults [24]. Those might explain why children were more sensitive to the combined treatment than adults.

Data analysis of laboratory indicators also supported the view that immunosuppressants combined with steroids were a superior alternative. It was generally believed that the massive proteinuria and hypoalbuminemia contributed to kidney disease progression and decreasing proteinuria and increasing the concentration of serum albumin were of great help for the recovery. Our study found that immunosuppressants plus steroids had an advantage on reduction of proteinuria (SMD = 0.28; CI 0.05–0.52,  $P = 0.019$ ) and improvement in serum albumin (SMD = 0.98; CI 0.35–1.60,  $P = 0.002$ ).

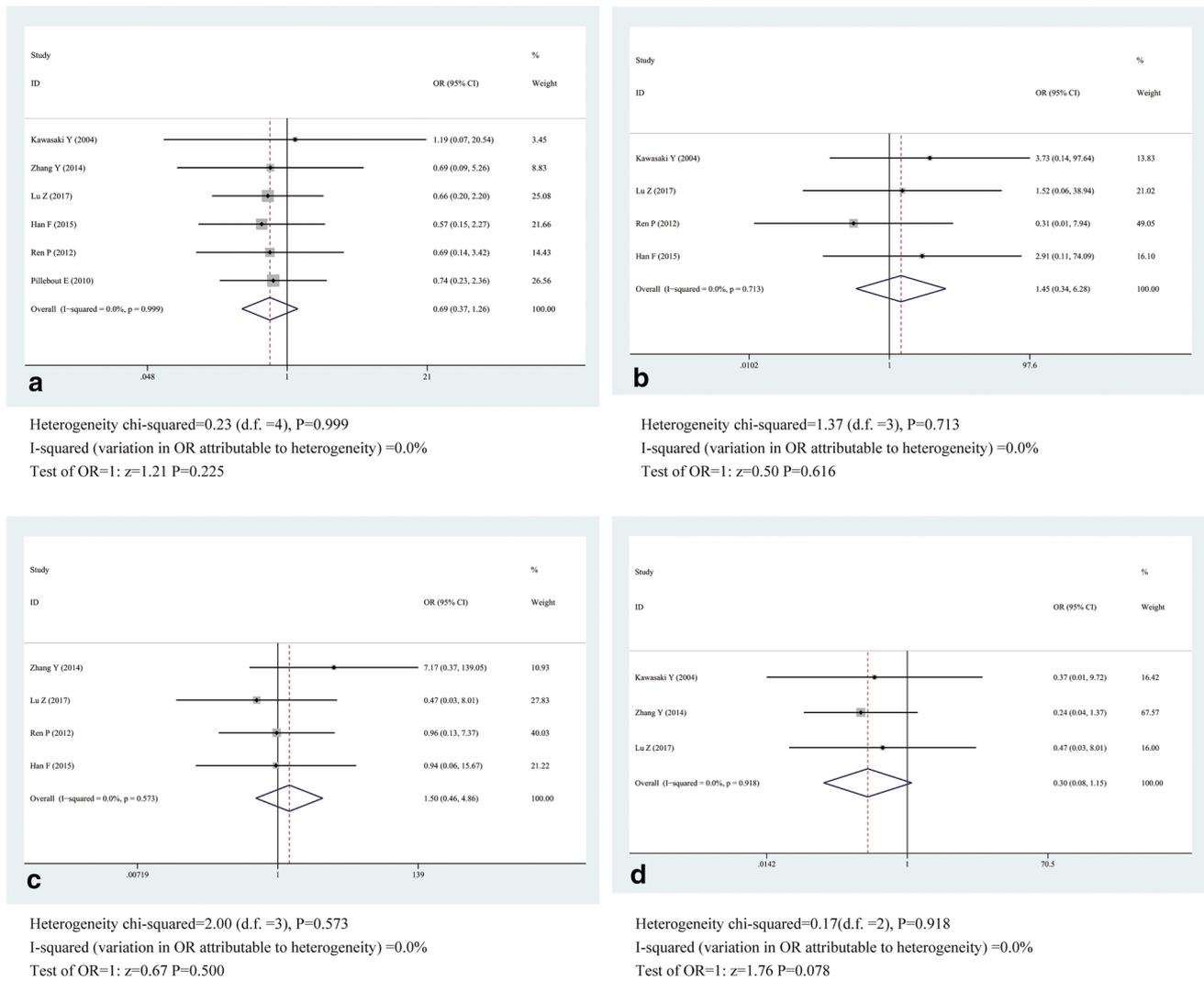


**Fig. 5** Meta-analysis on the laboratory indicators, including reduction of proteinuria (**a**), improvement in serum albumin (**b**), increasing level of eGFR (**c**), and endpoint level of eGFR (**d**)

However, no evidence proved that immunosuppressants could improve eGFR more effectively (SMD = 0.39; CI -0.20–0.97,  $P = 0.192$ ,  $I^2 = 73.7\%$ ). Notably, the heterogeneity was too large to neglect. Different conditions of the patients, different immunosuppressants, and different treatment options could contribute to the heterogeneity. Therefore, our study also analyzed the endpoint level of eGFR and found that patients seemed to have a slightly higher level of eGFR after the combined therapy (SMD = 0.21; CI -0.05–0.48,  $P = 0.110$ ). On the one hand, a total of 5 studies had demonstrated effects of combined therapy on eGFR, 4 of which were about adults. As is known, adult patients with HSPN usually have serious condition and they may be less sensitive to immunosuppressants. On the other hand, although eGFR is an important laboratory indicator to reflect kidney function, the importance becomes less to compare patients within normal limits. The point to emphasize here

was that the average of the baseline eGFR of patients in each study was greater than 110 ml/min/1.73 m<sup>2</sup>, except two with the mean eGFR < 70 ml/min/1.73 m<sup>2</sup>, 1 of which revealed that leflunomide added into steroids could improve the level of eGFR significantly (13, 20). Thus, more patients with renal dysfunction need to be researched to further analyze whether immunosuppressants combined with steroids could protect the renal function.

Eight retrospective studies and 1 prospective study were included in our meta-analysis. To eliminate the heterogeneity of experimental methods, all retrospective studies were analyzed and we arrived at the same conclusion. Our subgroup analysis also revealed that azathioprine combined with steroids was a better regimen for children who suffered from HSPN (OR = 6.67; 95% CI 1.33–33.36,  $P = 0.021$ ), while the treatment of mycophenolate mofetil plus steroids was as effective as steroids alone (OR = 1.28; 95% CI



**Fig. 6** Comparison of the rates of side-effects between both groups, consisting of infection (a), leukopenia (b), abnormal liver function (c), and hypertension (d)

0.59–2.75,  $P = 0.530$ ). But a small sample RCT has been carried out in children to investigate whether there was a difference between mofetil mycophenolate plus steroids and azathioprine plus steroids. The outcome presented that there seemed to be more remissions of urine protein in mofetil mycophenolate group, but no statistically significant differences were found, which suggested that the curative effects of the two regimens were comparable [25]. Our study failed to come to an exact conclusion that mofetil mycophenolate was a better choice, because the patients treated with mofetil mycophenolate included children and adults simultaneously in our selected articles and heterogeneity in clinicopathologic features and drug dosages did exist. Consequently, high-quality evidence is required to confirm the results.

It is worth mentioning that the outcomes of some other studies are consistent with ours, which were not included in

our manuscript due to the exclusion criteria. Edström H S et al. retrospectively analyzed that treatment with cyclophosphamide and steroids was effective to reduce urine protein and improve GFR in both IgAN and HSPN patients despite the severe clinical manifestations and advanced findings of renal biopsy [10]. Foster B J et al. also concluded that azathioprine combined with prednisone could prevent the progression of HSPN and was an efficient therapy compared with other regimens which was not specified in this study [11]. Additionally, a multicenter retrospective survey which treated adult patients with HSP, consisting of renal involvement and other visceral symptoms, was carried out to compare the prognosis of steroid regimens with or without cyclophosphamide. The multivariable logistic regression model used in this study found that the difference between combined therapy group and steroids group was not statistically

significant (OR = 0.88, 95% CI 0.29–2.67,  $P = 0.82$ ) but the fact that combined therapy was more beneficial was proved by inverse probability weighting on propensity score (OR = 1.79, 95% CI 1.00–3.20,  $P = 0.049$ ). So, the results turned out that steroids alone could be used as a first-line treatment for HSP but the efficacy of adding cyclophosphamide to steroids was still not clear [26]. Considering that glomerulonephritis is the most severe complication in HSP patients, it is quite reasonable to think that HSPN patients are more likely to benefit from the aggressively immunosuppressive treatment.

There are certain limitations in our study. Owing to lack of RCTs, most of literatures included in this meta-analysis were retrospective. Therefore, selection bias, information bias, and confounding bias could not be neglected. Our study failed to get the original data of individual patients and heterogeneity in clinicopathologic features, drug dosages, and definitions of remissions might influence the outcome. Notably, some baseline data could not be completely comparable due to the retrospective studies. But this had little effect on the result, because the baseline data presented in Table 2 indicated that patients who had severe clinicopathological symptoms were treated by more radically immunosuppressive treatments. The favorable outcome of these patients provided a further proof that immunosuppressive agents combined with steroids were a superior treatment. Furthermore, the number of studies is not sufficient for the efficacy of specific immunosuppressive agents and the data synthesized in this study were mostly from a single center with a small sample size. Hence, long-term, high-quality, large-sample, multicenter RCTs are required to make the research results more convincing.

In conclusion, based on the published articles, we concluded that the efficacy of the administration of immunosuppressive agents combined with steroids was more effective than that of steroids alone. The co-treatment has a greater impact on reducing proteinuria and improving serum albumin. Meanwhile, the side-effects of combination therapy are as tolerable as steroids, or even less. Since the more intensive immunosuppressive treatment of HSPN would raise the possibility of remission or the other endpoints, addition of immunosuppressive agents to steroids might be recommended in treating HSPN patients, especially for the pediatric population who are with severe HSPN or unresponsive to steroids. In order to make the conclusion more convictive, more high-quality trails are needed to ascertain our findings.

### Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interest in this manuscript.

**Research involving human and animal participants** This article does not contain any studies with human participants performed by any of the authors.

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