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NEPHROLOGY - ORIGINAL PAPER

Long-term efficacy of tonsillectomy as a treatment in patients with IgA nephropathy: a meta-analysis

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Abstract
Purpose IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide and will lead some unfavorable outcomes such as end-stage renal disease. The efficacy of tonsillectomy remains controversial in both Asian and Caucasian ethnicity. Our meta-analysis was aiming at exploring its long-term efficacy and providing further evidences for clinical treatment.
Methods Prospective and retrospective studies that compared the rate of clinical remission and/or end-stage renal disease in IgAN patients who applied tonsillectomy were involved in our meta-analysis. The online databases we searched were PubMed, Embase, Cochrane Library, and Web of Science
Results Nineteen studies with a total of 3483 participants are involved in our meta-analysis. It is found that treatment of tonsillectomy is significantly associated with a higher rate of clinical remission (15 studies, 3059 participants; pooled OR 3.30, 95 % CI 2.47–4.40). Meanwhile, tonsillectomy shows positive effect on refraining from developing end-stage renal disease (9 studies, 1804 participants; pooled OR 0.33, 95 % CI 0.16–0.69). In following two subgroup analyses, we integrate studies with more than 5 years of follow-up from clinical remission group and end-stage renal disease group. Both of them show that tonsillectomy has favorable long-term efficacy, pooled OR 3.37 (95 % CI 2.68–4.24) and 0.20 (95 % CI 0.12–0.33), respectively.
Conclusions Long-term efficacy of tonsillectomy indicates that this treatment is helpful in inducing clinical remission and inhibiting development of end-stage renal disease in patients with IgAN and should be considered for addition into standard clinical treatment.

Keywords IgA nephropathy · Glomerulonephritis · Tonsillectomy · Clinical remission · End-stage renal disease · Meta-analysis

Introduction

IgA nephropathy (IgAN) is the most prevalent glomerulonephritis worldwide and 30–40 % patients will suffer end-stage renal disease (ESRD) in 20 years after diagnosis [1–3]. Various treatments, expecting an improvement in long-term renal outcome, have been applied in IgAN patients, such as steroid pulse (SP), immunosuppressive agents, renin–angiotensin–aldosterone system (RAAS) inhibitors, and angiotensin-converting enzyme inhibitors (ACEI) [4–8]. To date, steroid pulse cycles followed by oral steroids seem to be relatively effective in some patients [6]. Meanwhile, immunosuppressive agents still remains uncertain [9].

Rasche et al. [10] firstly indicated that tonsillectomy could be used in patients with IgAN as a single treatment,

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and it was potentially associated with occurrence of ESRD in European patients. Hotta et al. [11] reported a remarkable effect of tonsillectomy plus steroid pulse (TSP) therapy on the remission of urinary abnormalities (clinical remission) in Asian patients. Kawasaki et al. [12] demonstrated that they successfully induced clinical remission (CR) in 11 patients who had been resistant steroid therapy and suggested that TSP might be a solution for steroid-resistant patients. In addition, clinical practice found that hematuria and tonsillitis always appeared at the same time period in IgAN patients, and chronic/recurrent tonsillitis was contributed to new onset and progression of IgAN [13]. Under modern clinical circumstances, the top priority of IgAN treatment is still inducing CR and preventing patients from developing ESRD. To date, tonsillectomy has already become a popular process to treating IgAN in both Asian and Caucasian patients, but clinical studies that compared tonsillectomy and rate of CR/ESRD yielded inconsistent consequences [8, 10, 11, 14–31]. Thus, we set up this meta-analysis to evaluate the efficacy, especially the long-term efficacy, of tonsillectomy in treating IgAN and tried to provide further evidences for clinical practice.

Materials and methods

Data searches and identification of relevant studies

Four databases including Embase, Cochrane Library, PubMed, and Web of Science were searched up to September 6, 2016 to identify relevant studies. The search strategy was based on combinations of key words: "IgA nephropathy", "glomerulonephritis", "tonsillectomy", "clinical remission", "end-stage renal disease", and "steroid pulse" without language restrictions. Authors of studies that we recruited would be contacted for further support when their articles contained incomplete information.

The selected studies should meet the following criteria: (1) study design was a prospective or retrospective cohort study or a controlled clinical trial; (2) study compared clinical outcomes (CR and/or ESRD) between patients with and without tonsillectomy; (3) study population was biopsy-proven IgAN patients. In this meta-analysis, the definition of CR was disappearance of urine abnormalities or one of these conditions: (1) RBC in urinary sediments <5 per high-power field; (2) proteinuria less than 0.3 g/24 h or 0.3 g/gCr; (3) remission of both proteinuria and hematuria. ESRD was defined as a patient appeared one of these conditions: (1) a serum creatinine level over 707 μmol/L or 8 mg/dL; (2) the initiation of dialysis therapy; (3) kidney transplantation. Reviews, simply commentaries, case reports, and unpublished reports were excluded.

Data extraction

Two investigators (Jiayu Duan and Dongwei Liu) extracted all the data independently and achieved consensus on all relevant items. Information extracted from each study included: (1) name of first author, (2) year of publication, (3) characteristics of study group, (4) study design, and (5) clinical outcome.

Study quality assessment

Assessment was accomplished independently by two investigators (Jiayu Duan and Dongwei Liu). For cohort study and case–control study, we scored each one by using Newcastle–Ottawa Quality Assessment Scale (NOS) [32]. For RCT study, we assessed them by following Cochrane criteria (showed in Table 1) [33].

Statistical analysis

The odds ratios (OR) and 95 % confidence interval (CI) were calculated for each study based on the number of patients who achieved CR or ESRD. Cochran's Chi-square-based Q statistic test was used to estimate heterogeneity between studies. It was considered statistically significant when $P < 0.1$. In this case, a random-effects model, using DerSimonian and Laird method, was further applied to calculate the pooled OR. Otherwise, a fixed-effects model, using Mantel–Haenszel method, was employed. A meta-regression was applied to explore the sources of heterogeneity across studies. The presupposed items for evaluation

Table 1 Risk of bias

Study	Adequate sequence generation	Adequate allocation concealment	Address incomplete outcome data	Selective outcome reporting	Free of other bias
Kawamura	No	Yes	Yes	No	Yes
Katafuchi	No	Yes	Yes	No	Yes
Yang	Yes	Yes	Yes	Unclear	Yes

"Yes" means low risk of bias; "No" means high risk of bias; "Unclear" means a proper judgment couldn't be made

None of these outcomes was reported by independent blind assessment

of heterogeneity sources were characteristics of each study such as number of patients, follow-up years and baseline of kidney function et al. A subgroup analysis was applied when the source was detected. Publication bias was evaluated by funnel plot and regression test. All *P* values were from two-tailed test with a significant level at 0.05 expect heterogeneity (mentioned before). All statistical analysis in this meta-analysis was carried out using Stata, version 12.0 (StataCorp LP).

Results

Characteristics of involved studies

After comprehensive search, 298 potential relevant articles were screened, of which, 279 articles were removed because of multiple reasons (Fig. 1). Thus, a total of 19 studies including 3483 participants were finally involved in this meta-analysis. Characteristics of participants and

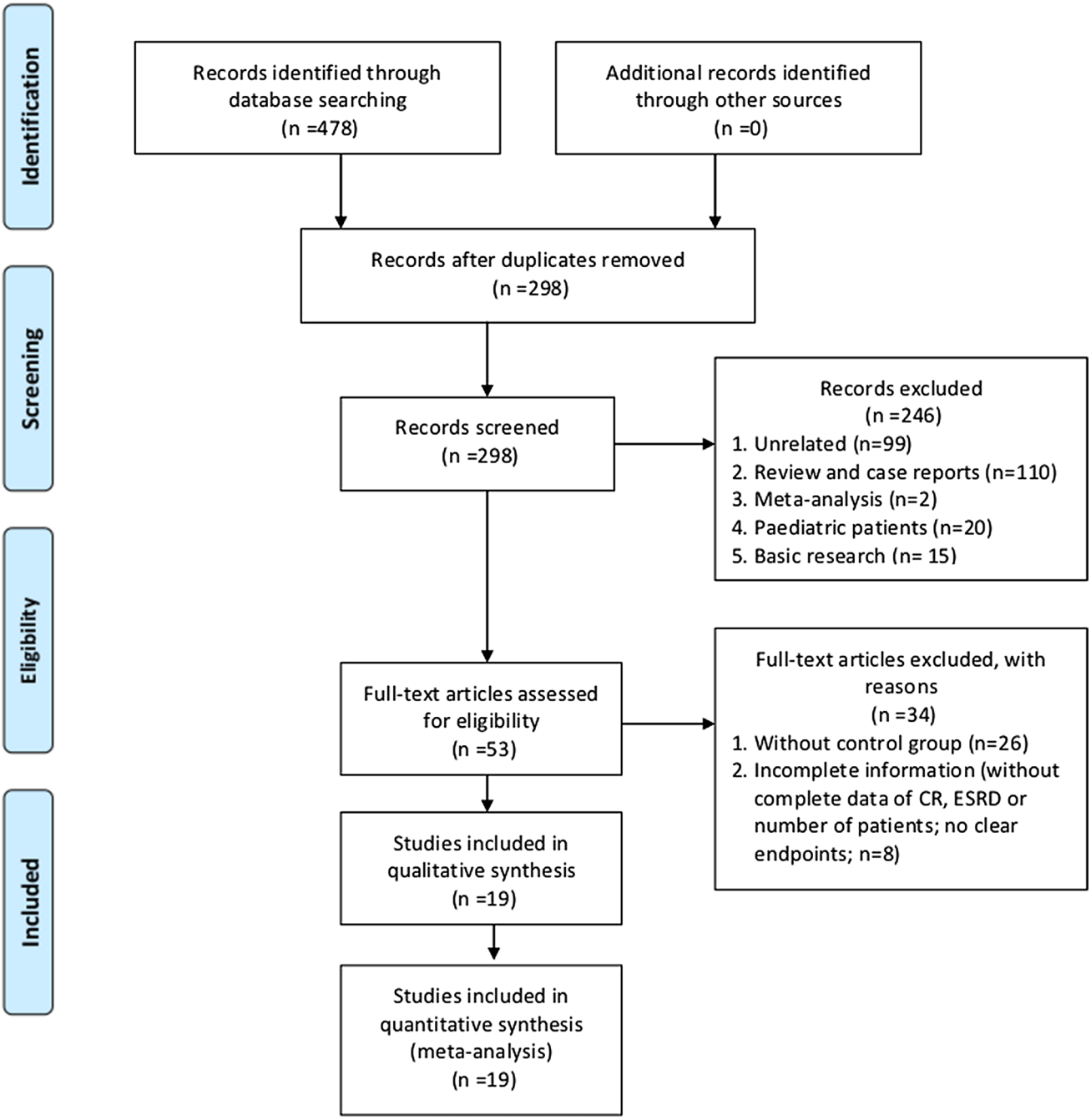

Fig. 1 PRISMA flow chart of study selection

Table 2 Characteristics of involved studies

First author	Study design	No. of patients (T/NT)	Age (years)	Gender (M/F)	Treatment		Duration (years)	CR (T/NT)	ESRD (T/NT)	NOS score
					Intervention	Control				
Rasche	RCS	55 (16/39)	29.0	16/39	TSP	No T	3.4	–	10/14	7
Hotta	RCS	329 (250/79)	36.1	119/210	TSP	No T	6.9	114/12	–	8
Sato	RCS	70 (30/40)	46.5	33/37	TSP	CS or general therapy	5.9	–	4/14	8
Xie	RCS	118 (48/70)	32.3	38/80	TSP	No T	16.1	–	5/18	8
Chen	RCC	112 (54/58)	27.3	31/81	TSP	SP	10.8	25/16	2/7	8
Miyazaki	PC	101 (78/23)	34.4	35/66	TSP	SP or T or general therapy	5.0	52/10	–	8
Komatsu	PNC	55 (35/20)	34.5	19/39	TSP	SP	4.5	19/5	0/1	7
Kawaguchi	RCS	388 (240/148)	34.3	133/255	TSP	SP or T or general therapy	8.3	186/59	–	8
Maeda	RCS	200 (70/130)	31.7	63/137	TSP	SP	5.2	24/12	–	8
Ochi	RCS	41 (26/15)	31.1	13/28	TSP	SP	1.0	18/2	–	7
Ohya	RCS	62 (41/21)	34.6	20/42	TSP	SP	5.8	24/10	–	8
Kawamura	RCT	72 (33/39)	38.2	28/44	TSP	SP	1.0	32/36	–	–
Feehally	CC	136 (44/92)	36.0	69/67	TSP	ACEI or ARB, SP	4.1	–	3/11	7
Hoshino	MCS	1127 (209/918)	44.1	638/489	TSP	SP or RASI	8.3	180/640	7/146	8
Miyamoto	RCS	284 (161/123)	37.3	123/161	TSP	CS	4.1	92/49	–	7
Katafuchi	RCT	59 (27/32)	39.0	27/32	TSP	SP	4.8	12/9	–	–
Komatsu	MCS	79 (46/33)	34.9	31/48	TSP	SP or T	4.7	33/14	0/1	7
Yang	RCT	98 (49/49)	30.0	45/53	TSP	SP	4.0	47/25	–	–
Hoshino	RCS	52 (26/26)	32.6	18/34	TSP	oPSL	6.0	15/11	5/21	8

Unless especially indicated, values are given as mean

RCS retrospective cohort study, *RCC* retrospective case–control study, *PC* prospective cohort, *PNC* prospective nonrandomized controlled, *RCT* randomized controlled trial, *CC* case–control study, *MCS* multicenter cohort study, *T* tonsillectomy, *SP* steroid pulse, *TSP* tonsillectomy plus steroid pulse, *CS* conventional steroid, *RASI* renin–angiotensin system inhibitor, *ACEI* angiotensin-converting-enzyme inhibitor, *ARB* angiotensin receptor blocker

studies were summarized in Tables 2 and 3. Except a European and a Caucasian study group, all of the others were Asian participants, in which, 3 groups were Chinese and 14 groups were Japanese. Mean age of each study group were 27.3–46.5 years, and percentage of female participants were 43.39–72.72 %. Duration of follow-up ranged from 1 to 16.1 years. Data of serum creatinine levels (mg/dL), estimated glomerular filtration rates (mL/min/1.73 m^2) and proteinuria (g/day) in each study group were accorded with our protocol (Table 4, showed in supplementary material).

Clinical remission

Within all involved studies, 15 studies (including 3059 participants) compared the rate of clinical remission between patients with and without tonsillectomy. After integrating, the pooled OR is 3.30, 95 % CI 2.47–4.40 ($P < 0.001$, Fig. 2). This result statistically indicates that tonsillectomy is associated with a higher rate of inducing CR when being used in IgAN treatment.

Meta-regression was employed to detect the potential sources of between-study heterogeneity. A series of univariate models were applied by adding single covariate involving study design, ethnicity, number of participants and duration of follow-up in sequence. Then we found that duration of follow-up generated the between-study heterogeneity.

Considering of the long-efficacy of tonsillectomy, we designed a subgroup analysis involving 8 studies with over 5-years follow-up period. The pooled OR is 3.37 (with no evidence of significant heterogeneity, $P = 0.114$), 95 % CI 2.68–4.24 ($P < 0.001$, Fig. 3).

End-stage renal disease

A total of 9 studies compared the rate of ESRD between patients with and without tonsillectomy. The overall pooled OR is 0.33, 95 % CI 0.16–0.69 ($P < 0.001$, Fig. 4). To further investigate the long-term efficacy of tonsillectomy in developing ESRD, we designed our second subgroup analysis including 5 studies with over 5-year follow-up period. The pooled OR is 0.20 (with no evidence of significant heterogeneity, $P = 0.325$), 95 % CI 0.12–0.33 ($P < 0.001$, Fig. 5). Both results of overall and subgroup analyses indicate that tonsillectomy is highly associated with a lower rate of developing ESRD.

Table 3 Definitions of clinical remission and end-stage renal disease in the involved studies

Study	Clinical remission	End-stage renal disease
Rasche	–	The initiation of dialysis therapy
Hotta	Negative proteinuria and hematuria by dipstick and urinary erythrocytes of 4/high-power field or less	–
Xie	–	The initiation of dialysis therapy
Sato	–	Patients required hemodialysis or continuous ambulatory peritoneal dialysis
Chen	The amount of urine protein excretion <0.4 g/24 h, urine red blood cells <104/ml	The level of SCr > 707 μmol/l (8 mg/dL) or a dialysis therapy or renal transplantation
Miyazaki	Urinary blood cell count <5/high-power field	–
Komatsu	Disappearance of proteinuria and/or hematuria	–
Kawaguchi	Disappearance of urinary protein by dipstick and urinary erythrocytes less than 1/high-power field	–
Maeda	Normal dipstick examination of hematuria and proteinuria	–
Ochi	U-Prot <0.3 g/gCr and U-RBC <5/high-power field	–
Ohya	Disappearance of proteinuria and hematuria	–
Kawamura	Disappearance of proteinuria and/or hematuria	–
Feehally	–	eGFR < 15 ml/min/1.73 m^2
Hoshino	–	The initiation of dialysis therapy
Miyamoto	Remission of both proteinuria and hematuria	–
Katafuchi	Disappearance of both proteinuria and hematuria	–
Komatsu	Disappearance of hematuria and proteinuria	Renal replacement therapy
Yang	Proteinuria <0.3 g/24 h, RBC in urinary sediments <5 per high-power field	–
Hoshino	U-prot <0.3 g/gCr or <0.3 g/day and U-RBC <5/high-powered field	–

eGFR estimated glomerular filtration rate, *SCr* serum creatinine, *U-Prot* urinary protein, *U-RBC* urinary red blood cell

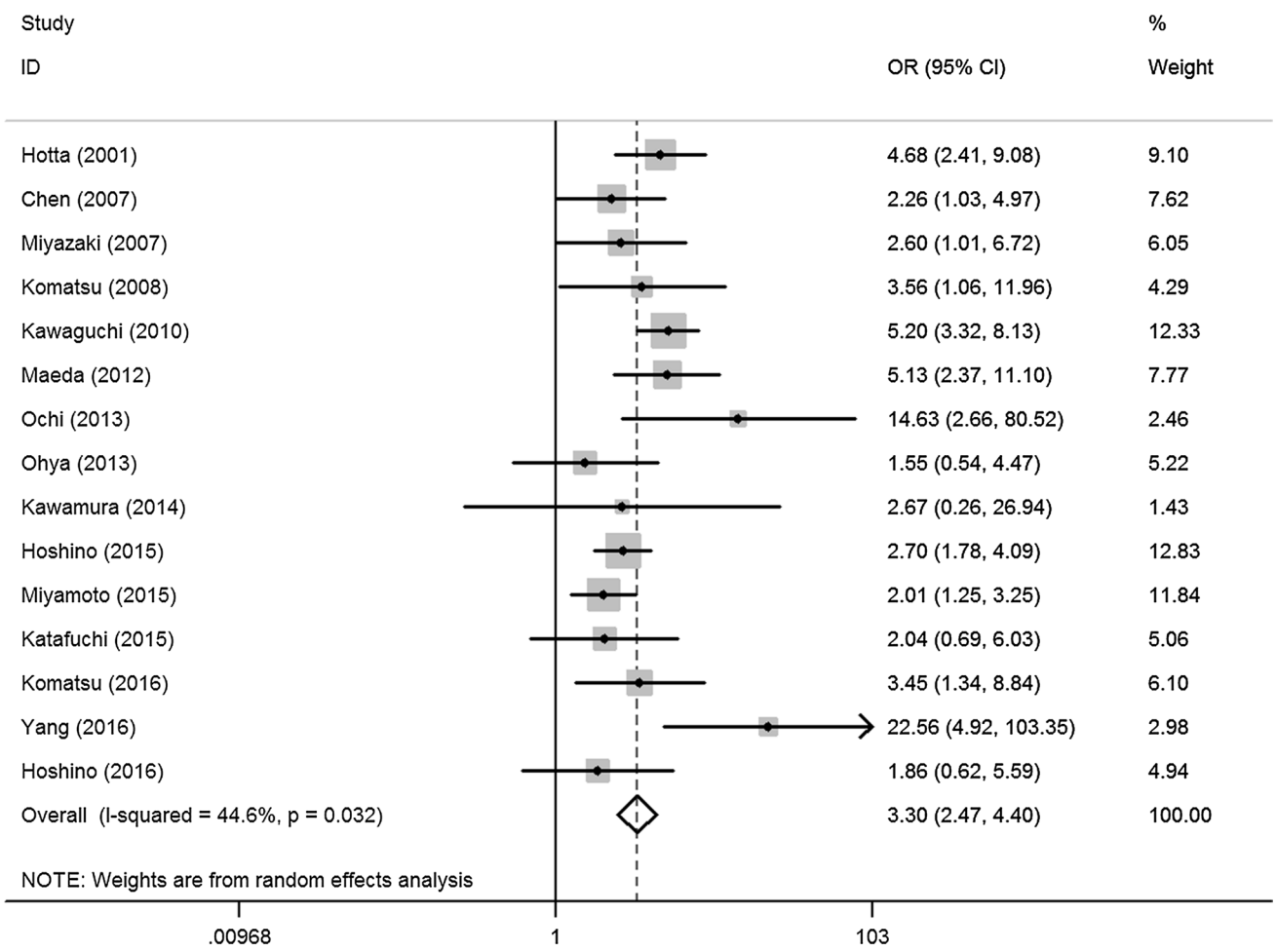

Fig. 2 Forest plot for the association between tonsillectomy and clinical remission in patients of IgAN

Sensitivity analysis and publication bias

To evaluate the effect of each single study on the pooled estimate, we performed 4 sensitivity analyzes for all of above meta-analysis. It turns out that all the results hardly changed after removal of each study, suggesting the robustness of our results (S. Figure 1–4, showed in supplementary material).

Publication bias was tested by funnel plot (Fig. 6a, b) and regression test. Dots in the funnel plot are mostly symmetrically distributed. The regression test further confirms that the publication bias hasn't detected in articles that reported CR and ESRD ($P = 0.536$, 0.580, respectively).

Discussion

Characterized by deposition of polymeric IgA, IgAN has become the most common glomerulonephritis in the world and its patients suffer multiple clinical symptoms besides hematuria and proteinuria. The frequent appearance of a combo of recurrent tonsillitis and hematuria generated the very first hypothesis that tonsillitis might be contributed to progression of IgAN because tonsils could produce underglycosylated IgA1. Recurrent antigenic stimulation caused by tonsils mucosal cells could lead to abnormal immune reactions in bone marrow, which results in the deposition of circulating immune complexes on mesangial cells and glomerular damage. Tonsillectomy could provide positive effects by cutting down a source of immune complex and reduce the damage of glomerular in IgAN [34]. Nevertheless, many studies that focus on the efficacy of tonsillectomy still have not turned out a consistent outcome.

To date, three RCTs, all of which involved in our meta-analysis, have evaluated the efficacy of tonsillectomy plus steroid pulse versus steroid pulse therapy. The first one, reported by Kawamura et al. [24], yielded that there was no significant difference between two treatments. But this trial had a relatively shorter follow-up period (1 year) which could not be used to evaluate the long-term efficacy of

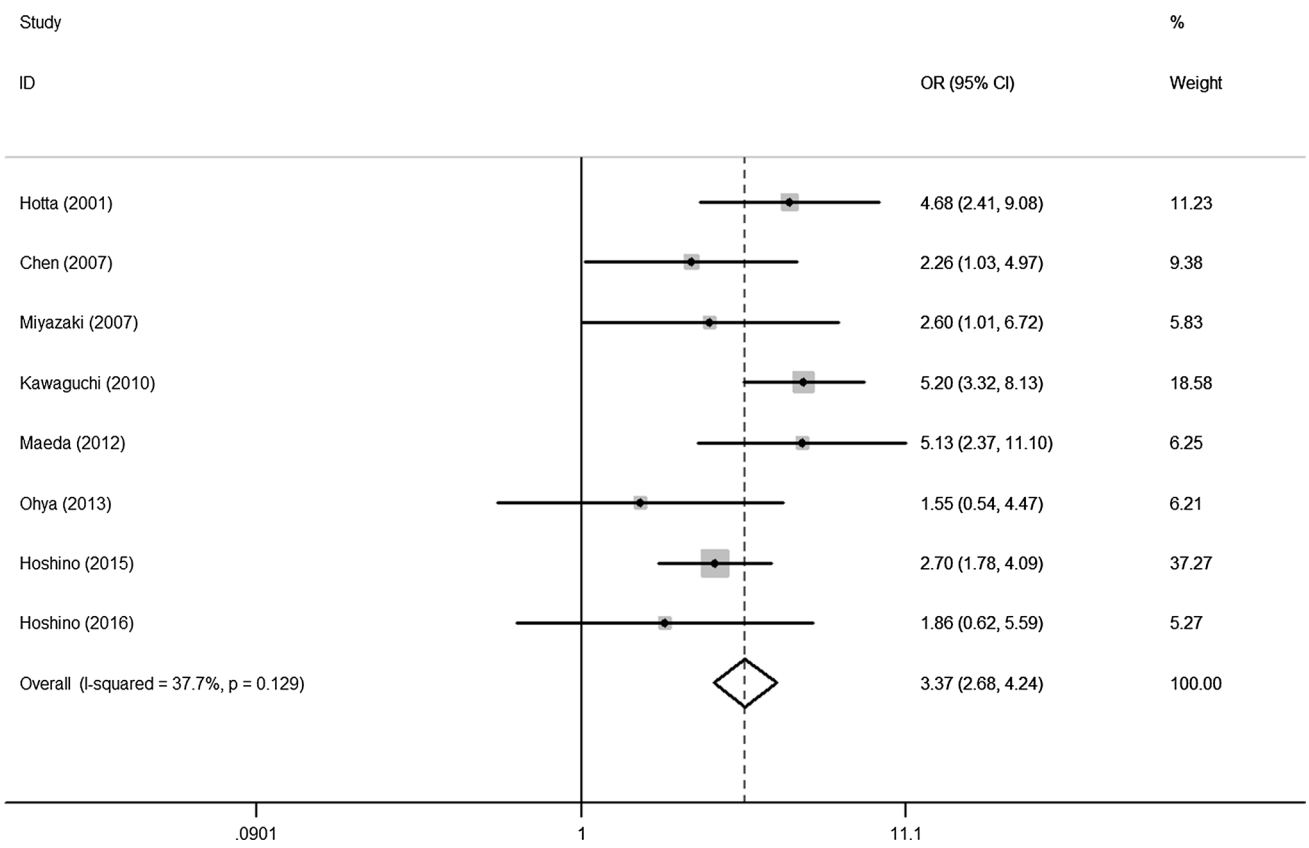

Fig. 3 Forest plot for the outcome of studies with over 5-years follow-up period in subgroup of clinical remission

tonsillectomy in clinical practice. The latest one, Yang et al. [30], demonstrated that tonsillectomy could be contributed to faster and longer remission in IgAN patients and its follow-up period was much more longer (4 years). Regarding differences between study participants and sample size of each study ($n = 72$, 59, 98, respectively), this circumstance is quite reasonable. Hence, more RCTs with large study sample are desperately needed in future to clarify whether tonsillectomy is valuable enough to be added in standard treatment of IgAN.

In this present study, we integrated 19 previous studies (involving three ethnicities) to evaluate the effect of tonsillectomy in IgAN treatment. Firstly, we analyzed the former results that compared CR's rate between patients with and without tonsillectomy. The value of pooled OR truly suggests that tonsillectomy plays a beneficial role in inducing CR. In our subgroup analysis, the pooled result of 8 studies indicates that tonsillectomy has a reliably long-term effect. Secondly, we investigated the potential impact of tonsillectomy on progression of ESRD. Both the overall result and our second subgroup analysis show that tonsillectomy has a positive effect on preventing patients from developing ESRD. Since the robustness of this meta-analysis had been evaluated by sensitivity analysis, the above results are considered stable and reliable.

Before that, we believe that our meta-analysis could provide multiple valuable evidences on effect of tonsillectomy for treatment of IgAN. Firstly, we integrated all of the latest studies including random clinical trial, case–control and cohort study. Therefore, we used two kinds of study assessment protocol (NOS and Cochrane) to evaluate the studies that involved in meta-analysis, which could ensure that all of them were fully qualified. Secondly, we not only integrated the relationship between tonsillectomy and CR's rate, but also analyzed its effect on ESRD. By removing studies with shorter follow-up period, our subgroup analysis could avoid influence and bias that came from short follow-up duration. As we mentioned before, over one-third of total patients would suffer ESRD in 20 years after diagnosis. It means that long-time period observation is very essential when evaluating treatments of IgAN. To our knowledge, this is the first time that a meta-analysis has focused the long-term efficacy on both of these clinical outcomes. Thirdly, in our two subgroup analyses, their results showed that there was no heterogeneity between studies, which means that all of the samples could be entirely

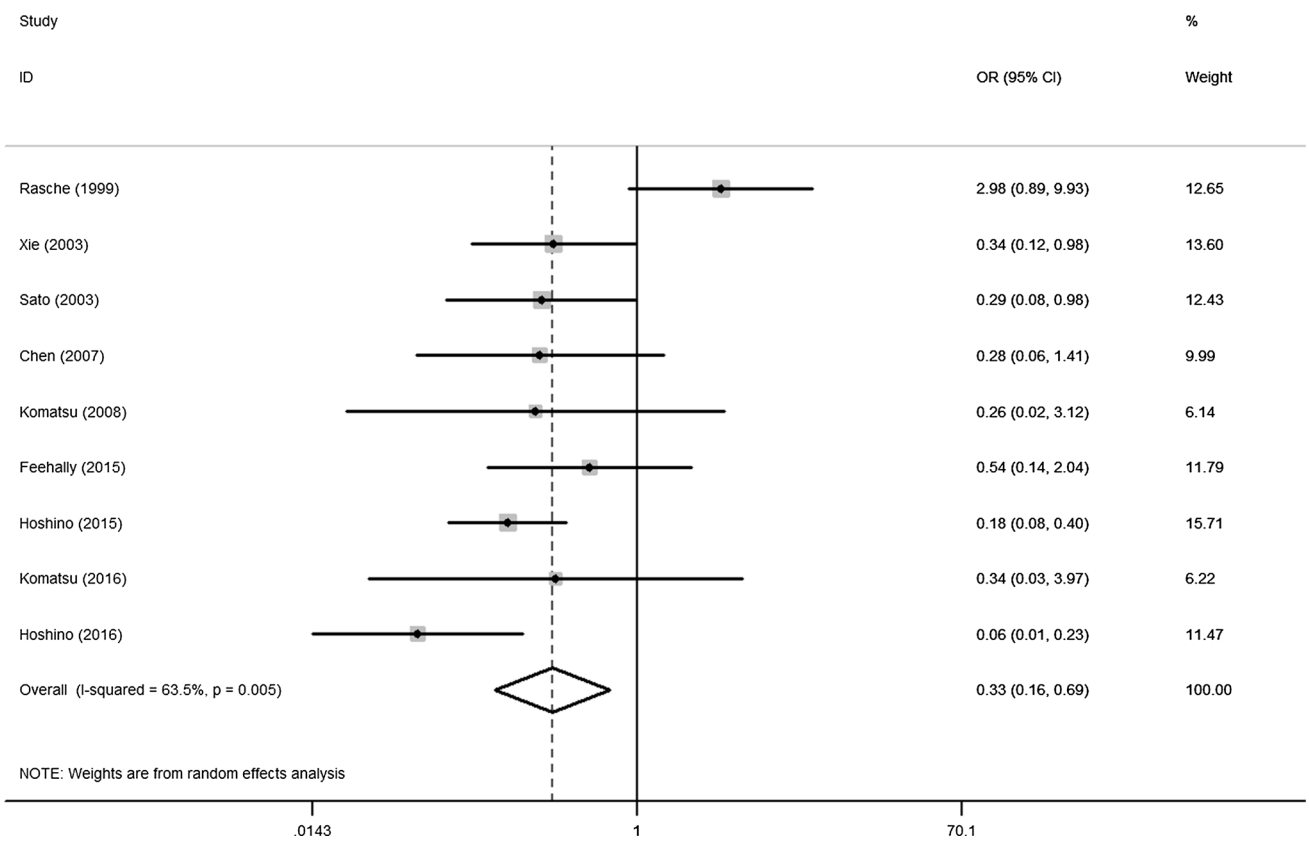

Fig. 4 Forest plot for the association between tonsillectomy and end-stage renal disease in patients of IgAN

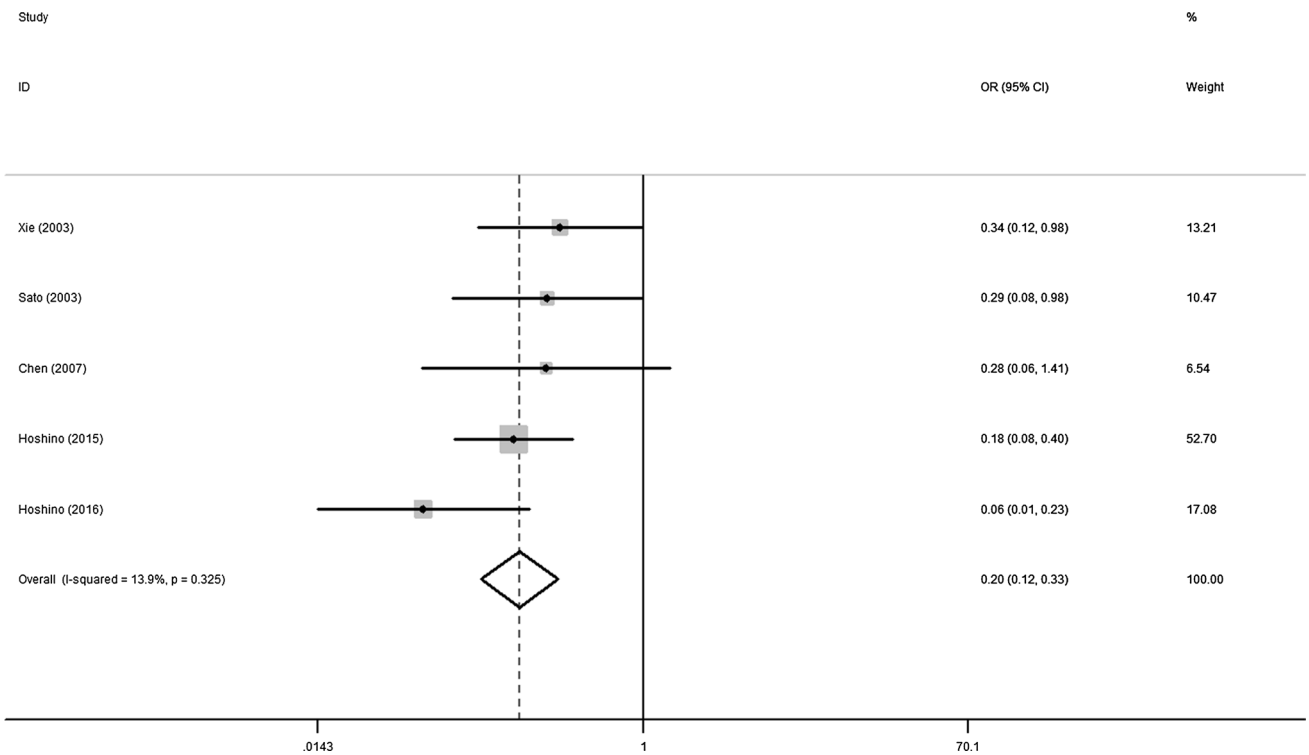

Fig. 5 Forest plot for the outcome of studies with over 5-years follow-up period in subgroup of end-stage renal disease

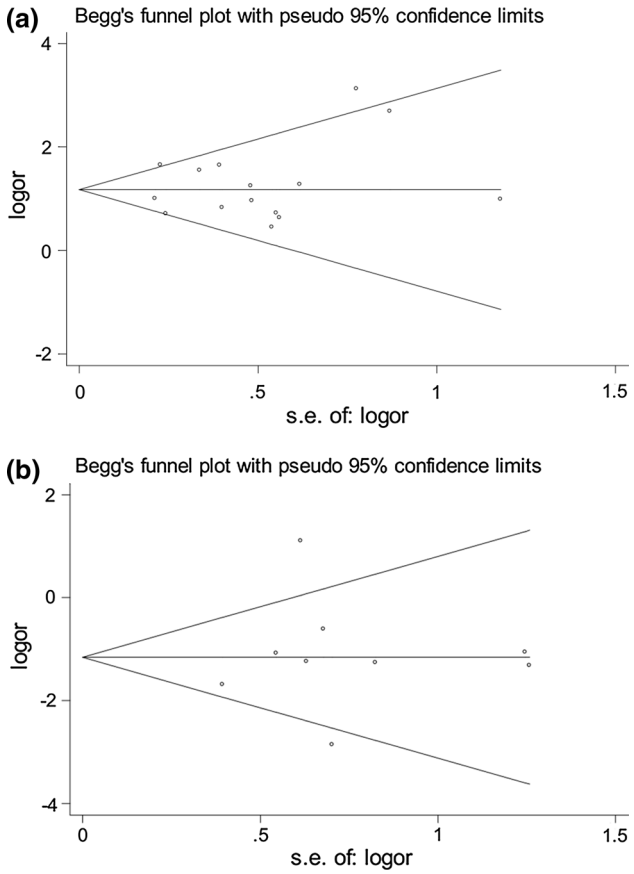

Fig. 6 **a** Funnel plot of natural logarithm of OR against inverse standard error in each study in clinical remission group, regression test for funnel plot asymmetry $P = 0.555$. **b** The funnel plot of natural logarithm of OR against inverse standard error in each study in end-stage renal disease group, regression test for funnel plot asymmetry $P = 0.803$

integrated and that made our meta-analysis more reliable than the other ones before.

Several limitations should be kept in mind when interpreting the results of this study. Firstly, lack of Caucasian study samples make our meta-analysis cannot deeply analyze the potential differences between ethnicities. Secondly, most of involved studies are retrospective studies. They may contain more confounding variables than RCT but we weren't able to adjust them properly. In addition, we wish we could analyze the effect between tonsillectomy and recurrence of IgAN.

In conclusion, this present study provides a credible evidence to support that tonsillectomy, especially under long-time treatment, and is significantly beneficial to inducing CR and protecting patients from developing ESRD in IgAN.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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