Comparative Evaluation of Tacrolimus and Cyclosporine in Patients with Steroid-resistant Nephrotic Syndrome: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: To date, several randomized trials have compared calcineurin inhibitors, especially tacrolimus, with cyclosporine in patients with steroid-resistant nephrotic syndrome, proposing conflicting results. Use of immunosuppressive therapy for the treatment of resistant nephrotic syndrome remains a matter of debate, and the evidence on its efficacy and safety is inconclusive. The present study aimed to compare the benefits and limitations of tacrolimus and cyclosporine in the treatment of steroid-resistant nephrotic syndrome.

Methods: This systematic review and meta-analysis was conducted via searching for the relevant trials performed until January 2018 in electronic databases such as PubMed, Scopus, ScienceDirect, Cochrane Library, and Web of Science. In total, 285 potentially relevant articles were identified, and four articles were selected for the review. A random effects model was used to analyze data, and the heterogeneity of the articles was assessed using Chi-square-based Cochran's Q and I2 statistics, and heterogeneity was considered statistically significant with I2>50%. The outcomes were presented as relative risk with 95% confidence interval, and P-value of less than 0.05 was considered statistically significant. In addition, meta-analysis was used for further data analysis.

Result: Awareness and knowledge are the main determinants of attitude in nurses, which should be applied in order to foster positive attitudes in the process of organ donation. Furthermore, extensive clinical knowledge should be acquired on organ donation and communication skills by ICU nurses through proper training programs.

Conclusion: In conclusion, Tacrolimus is superior to Cyclosporine in treating of patients with steroid resistant nephrotic syndrome in terms of no response to therapy, nephrotoxicity and hypertrichosis.

Introduction

Nephrotic syndrome is a common cause of chronic renal diseases across the world (1). Numerous patients with idiopathic nephrotic syndrome (INS) initially respond to steroid therapy. However, patients with frequently relapsing nephrotic syndrome, steroid-dependent nephrotic syndrome (SDNS) or steroid-resistant nephrotic syndrome (SRNS) require alternative treatments (2). Patients with SRNS are at the higher risk of disease complications, adverse reactions to drugs, and renal injury, while disease management is also more difficult in these patients (1). Furthermore, children who are resistant to first-line drugs may require immunosuppressive agents, such as calci-

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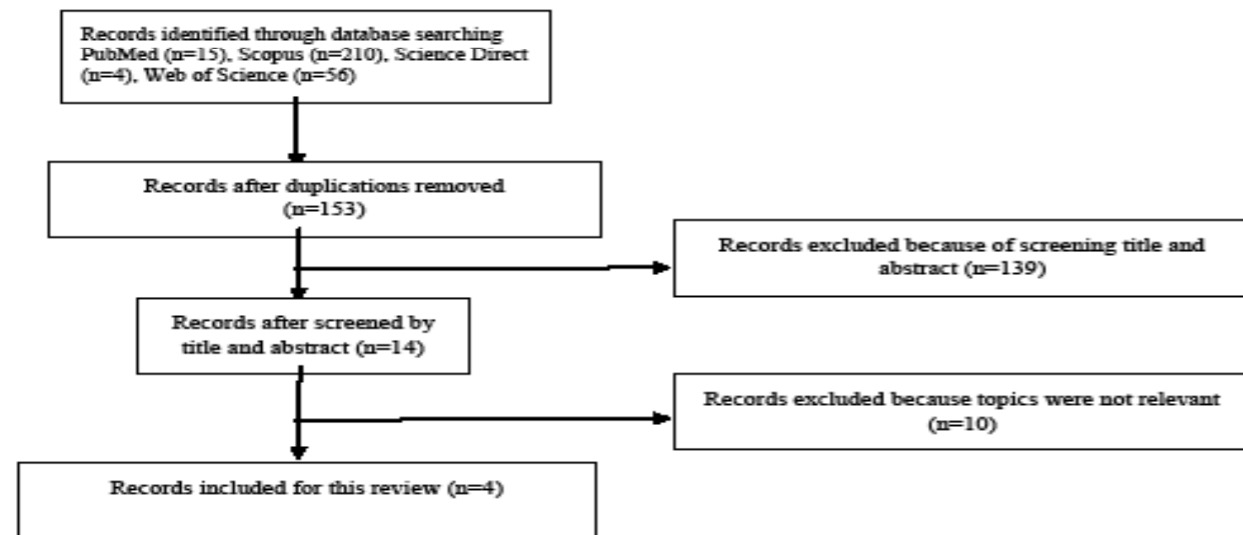E-mail: ravanshads@mums.ac.ir
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Figure 1. Flowchart of study selection process

Table 1. General Features of Systematically Reviewed Trials

First Author's Name	Year	Sample Size (patient)		Age (Year)		Gender Female/) (Male		Co-intervention both) (groups	Follow-up Duration (month)
		TAC (%) N	CYA (%) N	TAC	CYA	TAC	CYA		
.Li X	2008	(46) 12	(54) 14	22.7	31.7	4/8	5/9	Steroid	6
Choudhry	2009	(51) 21	(49) 20	75	62.6	7/14	9/11	Prednisolone + Enalapril	12
Wang	2012	(67) 50	(33) 24	8.6	7.7	17/33	6/18	Prednisone	24
Shah	2016	(51) 45	(49) 43	5.9	5.9	15/27	20/22	Steroid	6

TAC: tacrolimus, CYA: cyclosporine

Table 2. Response to Treatment in Patients Receiving CYA or TAC

First Author's Name	Year	Complete Remission		Partial Remission		No Response	
		TAC (%) N	CYA (%) N	TAC (%) N	CYA (%) N	TAC (%) N	CYA (%) N
.Li X	2008	(50) 10	(50) 10	(50) 1	(50) 1	(0) 0	(100) 2
Choudhry	2009	(47.6) 10	(52.4) 11	(66.6) 8	(33.3) 4	(37.5) 3	(62.5) 5
Wang	2012	(72) 44	(18) 17	(62.5) 5	(37.5) 3	(20) 1	(80) 4
Shah	2016	(54.6) 41	(45.3) 34	(11.1) 1	(88.8) 8	(0) 0	(0) 0

TAC: tacrolimus, CYA: cyclosporine

Table 3. Adverse Effects on Patients Receiving CYA or TAC

| First Author's Name	Year	Diabetes		InfectionS		Hypertension		ALT/AST Elevation		Gastrointestinal Symptoms		Hypertrichosis		Nephrotoxicity	
		TAC (%) N	CYA (%) N	TAC (%) N	CYA (%) N	TAC (%) N	CYA (%) N	TAC (%) N	CYA (%) N	TAC (%) N	CYA (%) N	TAC (%) N	CYA (%) N	TAC (%) N	CYA (%) N
.Li X	2008	NA	NA	(42.8) 3	(57.2) 4	(100) 1	(0) 0	(20) 1	(80) 4	(50) 2	(50) 2	NA	NA	NA	NA
Choudhry	2009	(0) 0	(0) 0	(50) 1	(50) 1	(0) 0	(0) 0	(45.4) 5	(54.6) 6	(85.7) 6	(14.3) 1	(0) 0	(100) 19	(40) 8	(60) 12
Wang	2012	(100) 1	(0) 0	(62.5) 15	(37.5) 9	(80) 12	(20) 3	(61.5) 8	(38.4) 5	(68) 11	(32) 5	NA	NA	(0) 0	(100) 4
Shah	2016	(0) 0	(0) 0	NA	NA	(41.6) 5	(58.4) 7	(0) 0	(0) 0	NA	NA	(2.9) 1	(97.1) 34	(0) 0	(100) 2

TAC: tacrolimus, CYA: cyclosporine
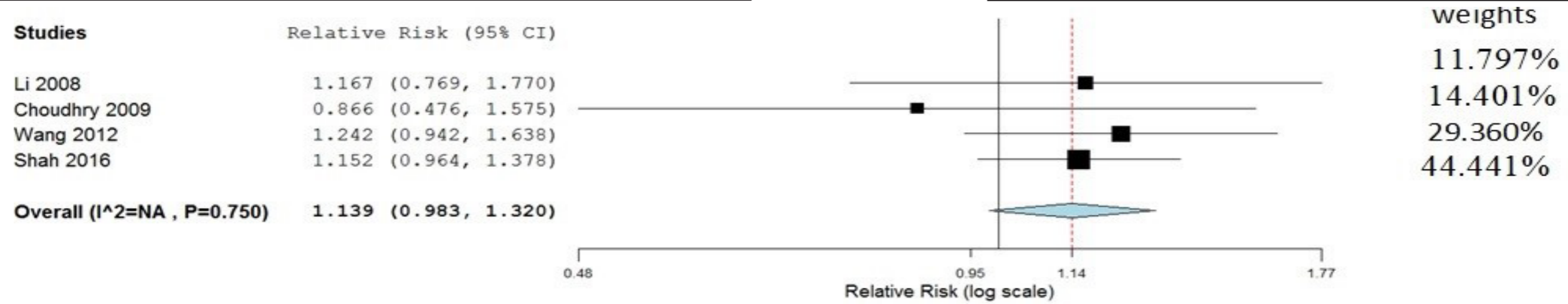
Figure 2. Forest plot of complete remission comparing two groups of intervention; tacrolimus versus cyclosporine
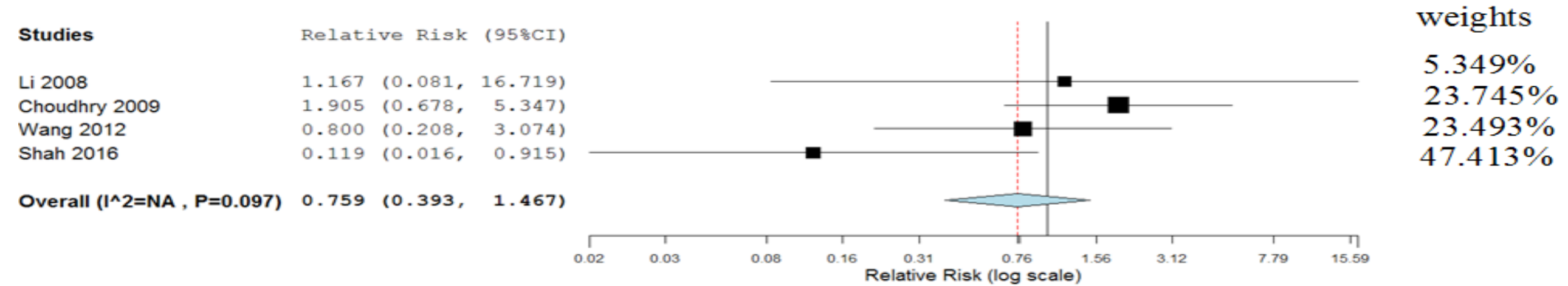

Figure 3. Forest plot of partial remission comparing two groups of intervention; tacrolimus versus cyclosporine
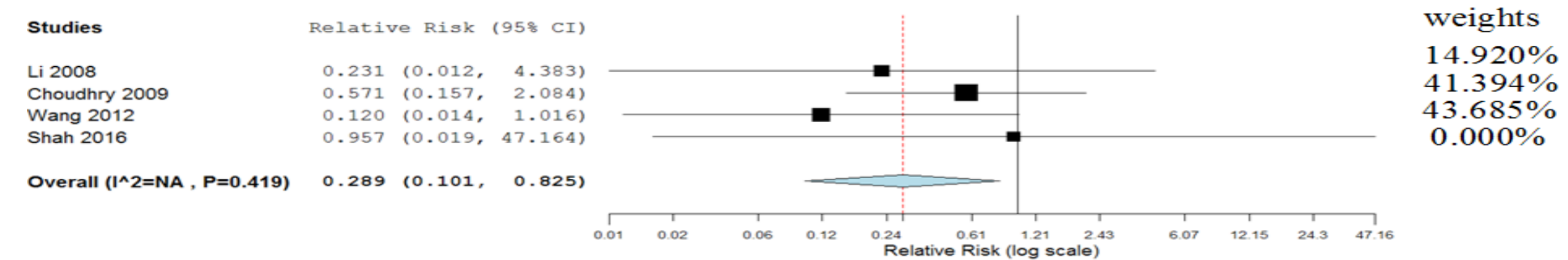

Figure 4. Forest plot of no response comparing two groups of intervention; tacrolimus versus cyclosporine
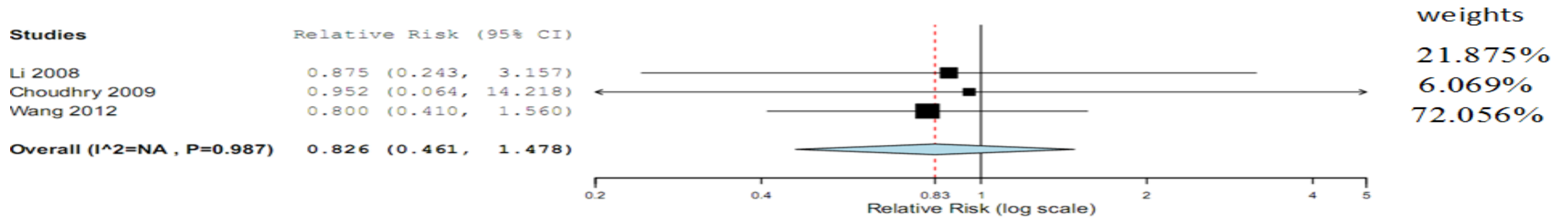
Studies   Relative Risk (95% CI)

Li 2008   0.875 (0.243, 3.157)
Choudhry 2009   0.952 (0.064, 14.218)
Wang 2012   0.800 (0.410, 1.560)

Overall (I^2=NA , P=0.987) 0.826 (0.461, 1.478)

weights
21.875%
6.069%
72.056%

Figure 5. Forest plot of infection comparing two groups of intervention; tacrolimus versus cyclosporine

Studies   Relative Risk (95% CI)

Li 2008   3.462 (0.154, 77.864)
Choudhry 2009   0.955 (0.020, 45.949)
Wang 2012   1.920 (0.597, 6.173)
Shah 2016   0.683 (0.234, 1.988)

Overall (I^2=0 % , P=0.543) 1.163 (0.550, 2.462)

weights
5.801%
3.746%
41.232%
49.221%

Figure 6. Forest plot of hypertension comparing two groups of intervention; tacrolimus versus cyclosporine

Studies   Relative Risk (95% CI)

Li 2008   0.292 (0.038, 2.268)
Choudhry 2009   0.794 (0.287, 2.194)
Wang 2012   0.768 (0.281, 2.100)
Shah 2016   0.957 (0.019, 47.164)

Overall (I^2=0 % , P=0.846) 0.708 (0.364, 1.377)

weights
10.519%
42.820%
43.749%
2.913%

Figure 7 : Forest plot of ALT/AST elevation comparing two groups of intervention; tacrolimus versus cyclosporine

Figure 8. Forest plot of gastrointestinal symptoms comparing two groups of intervention; tacrolimus versus cyclosporine

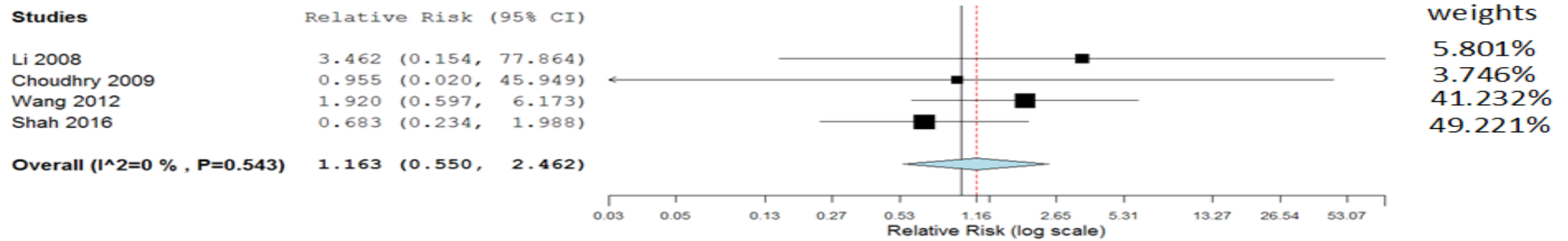**Figure 9.** Forest plot of nephrotoxicity comparing two groups of intervention; tacrolimus versus cyclosporine

Figure 10. Forest plot of hypertricosis comparing two groups of intervention; tacrolimus versus cyclosporine
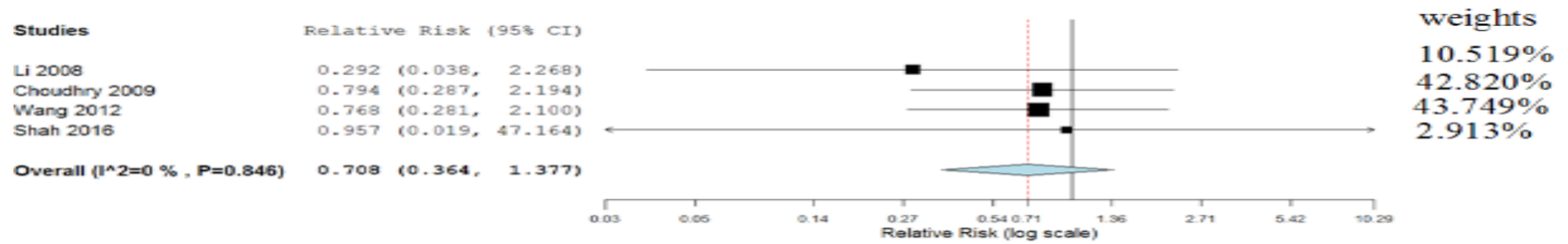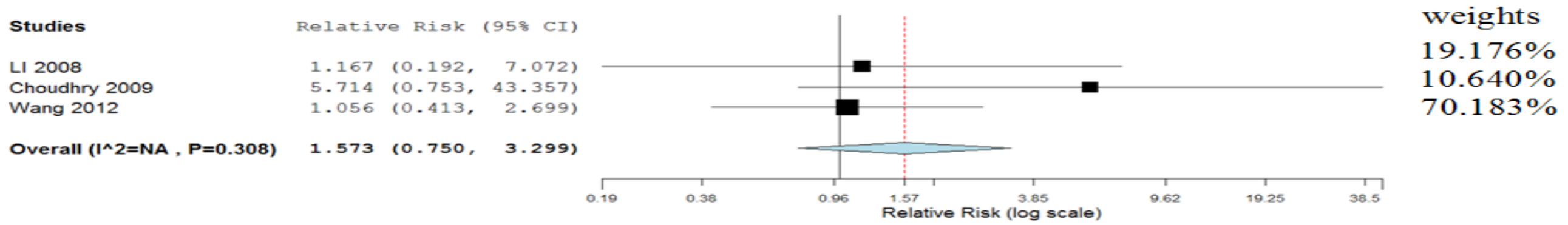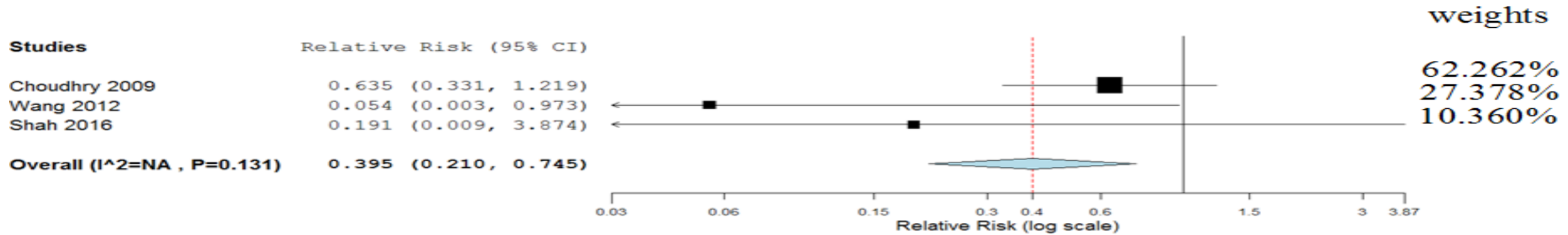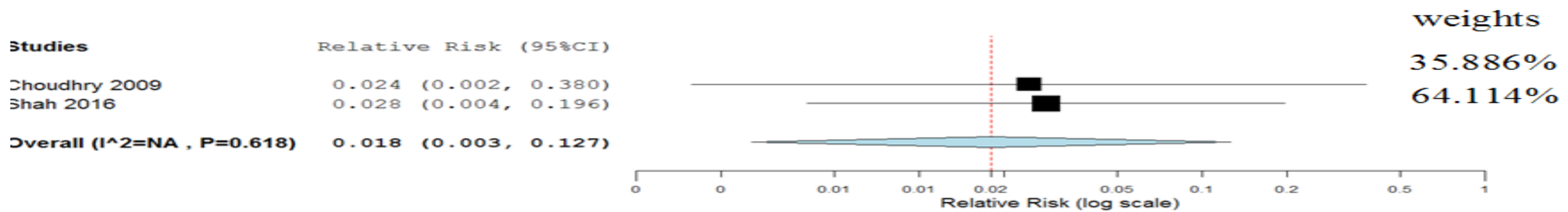
neurin inhibitors (e.g., cyclosporine or tacrolimus) and non-immunosuppressive drugs (e.g., angiotensin-converting enzyme inhibitors) (3).

Previous studies have reported remission in 50-60% of patients with SRNS (4). Therefore, the goal of the therapy should be the induction of remission using the medications that are associated with toxicity avoidance. Although clinicians have used various agents in the treatment of patients with SRNS, the optimal treatment regimen remains unclear (5). Tacrolimus (TAC) is classified as an immunosuppressive macrolide in the calcineurin inhibitor (CNI) group and is widely used after organ transplantation. Recent studies have indicated that the further effects of TAC on proteinuria result from the stabilization of the actin cytoskeleton or reduction of angiopoietin-like protein 4 levels in podocytes (6). Compared to cyclosporine (CYA), TAC has proven more potent in cytokine suppression and is associated with lower renal toxicity. CYA is also a type of CNI, which is effective in the management of SDNS, suggesting that other immunosuppressants targeting the calcineurin pathway may also be effective in the treatment of these patients (7).

Renal injury is a common concern regarding the use of CYA, which has been reported to depend on the dosage and cumulative usage time of the drug in previous studies (8). In order to reduce these side-effects, researchers have applied lower dosages of CYA (1.5-3 mg/kg/d) in some studies with small sample sizes, denoting its effectiveness in patients with idiopathic membranous nephropathy, with the remission rate reported to be 57.1-100% (9-11).

This systematic review aimed to compare the effectiveness of TAC and CYA in patients with SRNS.

Methods

This systematic review was conducted by two researchers via searching in electronic databases such as PubMed, Cochrane Library, ScienceDirect, Scopus, and Web of Science (updated until January 2018) using keywords such as cyclosporin* or CyA or Neoral* or Sandimmun*, Tacrolimus or FK506 or Prograf, "Steroid-resistant nephrotic syndrome", and random* or blind* or placebo* or meta-analysis. The bibliographies in the relevant articles and conference proceedings were scanned as well. In addition, the studies were assessed by the same author for the possible overlapping of the participant groups. If the study was reported to be a duplicate, we only included the most recent or complete study.

The eligibility criterion of the study was all the studies comparing TAC with CYA in the treatment of SRNS with any combination of other immuno-

suppressive treatments in both intervention and control groups.

Data Extraction and Quality Assessment

Data were extracted from the articles by two independent reviewers based on the selection criteria, and disagreements were resolved through discussions between the reviewers and considering the opinion of a third reviewer. The extracted data from the selected articles included the name of the first author, year of publication, study design, sample size, mean age of the patients, intervention regimen, duration of follow-up, concomitant treatments, and outcome measures in each study group. All the analyses were performed based on the previously published studies, and no ethical approval or patient consent was required.

Quantitative Data Synthesis and Data Analysis

The required data were extracted using comprehensive meta-analysis to pool the data for estimate summarization, and the relative risk of the results was expressed at 95% confidence interval. In addition, the heterogeneity of the selected studies was evaluated using Chi-square-based Cochran's Q and I2 statistics in order to measure the proportion of the total variation due to heterogeneity beyond chance. In case of I2>50%, heterogeneity was considered to be statistically significant. A random effects model was also used for data analysis. Otherwise, a fixed effects model was applied as the preferred method. In all the statistical analyses, P-value of less than 0.05 was considered significant.

Results

Search Results and Features

The literature search and reference mining yielded 285 potentially relevant articles. In total, 132 articles were eliminated due to duplication, and 139 articles were excluded after the review of the titles and abstracts since they were books, book sections, review papers or irrelevant. Afterwards, the full text of the selected articles was reviewed, and 10 articles were eliminated due to the irrelevance of the research subject. Finally, four studies were selected for the systematic review (1, 2, 5, 7). The flow diagram of article selection is depicted in Figure 1. The features and details of the studies are presented in Table 1.

Study Outcomes

Table 2 shows the summary of the study outcomes regarding the comparison of TAC and CYA.

Quantitative Synthesis

Complete Remission

Among the selected articles, four studies presented data on complete remission, and no significant difference was reported between TAC and CYA in terms of complete remission (RR=1.14; 95% CI: 0.98-1.32; P=0.08) (Figure 2).

Partial Remission

According to the findings, four studies presented data on graft loss, and no significant difference was denoted between TAC and CYA in this regard (RR=0.759; 95% CI: 0.393-1.47; P=0.413) (Figure 3).

Lack of Response to Therapy

According to the reviewed articles, lack of response to therapy was higher in case of CYA compared to TAC (RR=0.289; 95% CI: 0.101-1.47; P=0.02) (Figure 4).

Infections

In all the reviewed studies, the observed prevalence and type of infections were similar between the treatment groups (RR=0.826; 95% CI: 0.461-1.478; P=0.519) (Figure 5).

Hypertension

The reviewed findings denoted no significant difference in proportion of the patients with hypertension between TAC and CYA (RR=1.163; 95% CI: 0.550-2.462; P=0.693) (Figure 6).

Elevated ALT/AST Proportion

The pooled results indicated no statistically significant differences between TAC and CYA in terms of the increased ALT/AST proportion (RR=0.708; 95% CI: 0.364-1.377; P=0.309) (Figure 7).

Gastrointestinal Symptoms

The reviewed articles reported no significant difference in the proportion of the patients with gastrointestinal symptoms between TAC and CYA. (RR=1.573; 95% CI: 0.750-3.299; P=0.231) (Figure 8).

Nephrotoxicity

The pooled results demonstrated no significant difference between TAC and CYA in terms of nephrotoxicity (RR=0.395; 95% CI: 0.210-0.745; P=0.004) (Figure 9).

Hypertrichosis

Denoting a significant difference, the reviewed articles indicated that hypertrichosis is more prevalent with the use of CYA compared to TAC (RR=0.018; 95% CI: 0.003-0.127; P<0.001) (Figure 10). Table 3 shows these adverse effects on the patients receiving TAC and CYA in detail.

Discussion

According to the findings of this review study, TAC seems to be significantly superior to CYA in patients with SRNS in terms of the lack of response to therapy, nephrotoxicity, and hypertrichosis.

However, no significant differences were observed between these drugs regarding the infection rate, hypertension, ALT/AST elevation, and gastrointestinal symptoms.

In a meta-analysis, Elisabeth M. Hodson et al. assessed 19 randomized controlled trials (RCTs) regarding the risks and benefits of the interventions used in patients with idiopathic nephrotic syndrome with no remission after four weeks (or more) of daily corticosteroid therapy, concluding that calcineurin inhibitors increased the chance of complete/partial remission more significantly compared to placebo/no treatment or cyclophosphamide (3).

In another research in this regard, Yizhi Chen et al. reviewed 36 studies conducted on 1,825 patients in order to investigate the effects of immunosuppression on the adults with idiopathic membranous nephropathy (IMN) and nephrotic syndrome. Although the results of the mentioned study indicated that the 2012 KDIGO Clinical Practice Guideline recommended CYA or TAC as the alternative regimens for adult patients with IMN and nephrotic syndrome, no evidence was found regarding the fact that calcineurin inhibitors could alter the combined outcome of death or end-stage renal disease (12).

The results of another meta-analysis on the comparison of TAC and CYA in terms of immunosuppression after renal transplantation indicated that TAC is significantly preferred to CYA regarding graft loss, acute rejection, and hypercholesterolemia, while CYA seems to be significantly superior to TAC in diabetic patients (4).

Another meta-analysis regarding the effectiveness and safety of immunosuppressive medications in children with SRNS demonstrated that TAC and CYA should be favored as the first-line treatment for the pediatric patients experiencing SRNS owing to their high efficacy and generally favorable, albeit not superior, safety. In addition, TAC had similar effectiveness and was associated with the lower risk of secondary adverse events compared to CYA. Therefore, it was suggested that further well-designed RCTs be conducted to evaluate the relative benefits and limitations of TAC and CYA in pediatric patients with SRNS (13).

Conclusion

Despite the limitations of the present study due to the size and nature of the reviewed studies, our systematic review indicated that TAC is significantly superior to CYA in terms of the lack of response to therapy, nephrotoxicity, and hypertrichosis. It is recommended that further RCTs on larger sample sizes be performed in this regard.

Conflict of Interest

The authors declare no conflict of interest.

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