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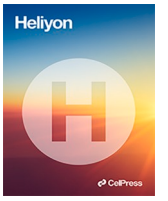

Research article

Meta-analysis of the adoption of omalizumab in the treatment of pediatric allergic diseases

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ABSTRACT

Introduction: Allergic diseases are common chronic conditions in children, omalizumab has a wide range of adoptions in various diseases. A meta-analysis was implemented to demonstrate the efficacy of omalizumab in the therapy of pediatric allergic diseases.

Materials and methods: English databases were searched. The search terms included "Omalizumab", "Children", "Allergic asthma", and "Atopic dermatitis". The literature was screened regarding inclusion and exclusion criteria, and data were extracted and analyzed using RevMan5.3.

Results: a total of six suitable studies, comprising 2761 patients, were selected for inclusion. The meta-analysis results implied that at 24 weeks, OR for worsening of symptoms in children was 0.10 (95 % confidence interval [CI] 0.03–0.41), Z = 3.24, $P = 0.001$ ($P < 0.05$); at 52 weeks, OR was 0.27 (95 % CI 0.09–0.83), Z = 2.28, $P = 0.02$ ($P < 0.05$); and during treatment, OR for adverse events in children was 0.87 (95 % CI 0.60–1.29), Z = 0.68, $P = 0.49$ ($P > 0.05$).

Conclusion: the study comprised six investigations that examined the effectiveness of omalizumab in treating pediatric allergic diseases. The findings demonstrated that, in comparison to standard treatment, omalizumab can greatly alleviate allergy-related clinical symptoms in children, slow down disease progression, and has a higher safety profile with fewer adverse reactions. These results have practical implications and highlight the potential value of omalizumab in pediatric allergy treatment.

1. Introduction

Allergic diseases are some of the most complex and prevalent conditions, including diseases such as urticaria, eczema, atopic dermatitis, and allergic rhinitis [1–3]. Allergic diseases often lack a clear allergen, and clinical symptoms may persist, making complete treatment and prevention difficult, causing great pain to patients and their families [4]. Allergic diseases are common chronic conditions in children, and sensitization to allergens is a major factor in their development. Common allergic diseases in children include eczema, urticaria, bronchial asthma, allergic rhinitis, and conjunctivitis [5,6]. For most children, these symptoms are mild, but in severe cases, they can cause disability or even threaten life. Allergic diseases are abnormal immune responses caused by allergen stimulation [7]. Imbalance in the immune system leads to allergic inflammatory responses, which are the main cause of allergic diseases. Genetic and environmental factors play a role in the development of allergic diseases, with environmental factors playing a

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major role [8]. Hence, detecting allergens in children's environment, avoiding contact with allergens, is extremely important for the prevention and treatment of allergic diseases. At present, there is no complete cure for allergic diseases, and treatment mainly focuses on symptom management. Nevertheless, identifying allergens and avoiding exposure to them is sometimes more important than treating symptoms [9].

The rational basis for using anti-IgE antibodies to treat immunoglobulin (Ig) E-mediated allergies has been envisioned. Nevertheless, mouse anti-IgE utilized *in vivo* has long been excluded due to allergic reactions to heterologous antibodies [10]. Nonetheless, mouse anti-IgE is commonly utilized *in vitro* to study the pathophysiology of allergy by blocking the release of mediators from eosinophils and mast cells. Eventually, the recombinant anti-IgE humanized monoclonal antibody-E25, now known as "omalizumab," was developed [11]. Based on its clinical use for severe asthma nearly twenty years ago, omalizumab demonstrates high efficacy and safety in treating severe asthma that can't be addressed by routine approach [12]. It is recognized as an adjunct therapy for uncontrolled asthma by global asthma initiative guidelines and is licensed to treat chronic spontaneous urticaria, although the optimal therapy duration for these two diseases has yet to be determined [13]. A large body of literature indicates that omalizumab has a broad range of adoptions in various diseases, regardless of whether the pathophysiology is allergic or non-allergic [14,15]. Hence, omalizumab may be a promising drug for children with uncontrolled allergic diseases.

Hence, a meta-analysis of this type of study was implemented to provide reliable evidence-based medicine for clinical practice. Meta-analysis is a methodology of summarizing results of multiple studies with the same research objective and analyzing and evaluating their combined effect sizes. Retrospective and prospective case-control studies were mainly included and analyzed to better evaluate and analyze the relationship between the two from the perspective of evidence-based medicine, thereby guiding clinicians to make more reasonable and accurate decisions.

2. Data and methodologies

2.1. Literature retrieval

A computer-based search of English databases such as PubMed, Web of Science, Embase, and The Cochrane Library was conducted, with the searching from the database establishment to April 2023. The terms included "Omalizumab", "Children", "Allergic asthma", and "Atopic dermatitis". These terms were combined in the optimal way to obtain the maximum amount of relevant literature. The search terms were limited to the title, keywords, and abstract, as well as references from searched articles were also traced. Furthermore, full-text articles were manually searched.

2.2. Criteria

Inclusion criteria: 1) Published literature on the use of Omalizumab in treating pediatric allergic diseases, with no restrictions on publication date and language limited to English; 2) Experimental groups receiving treatment with Omalizumab and control groups receiving placebo treatment; 3) Availability of original data on patient outcomes following treatment (number of exacerbations at 24 and 52 weeks, adverse events after medication use); 4) The literature must include a group treated with biologics and compared to other drug therapies.

Exclusion criteria: 1) Literature that lacks complete data; 2) Duplicate publications; 3) When the same institution reported the same target results in two studies, the higher quality report should be included; 4) Reviews or editorial articles; 5) Animal or cell experiments.

2.3. Literature quality evaluation

Two researchers conducted independent reading of the searched literature, requiring the full-text reading of each paper and extracting information. In cases of disagreement or dispute, discussion or the involvement of a third party was required for resolution. Jadad scale was adopted to assess study quality, including whether (1) the study was a randomized controlled trial, (2) randomization method was appropriate, (3) the study was double-blind, (4) blinding methodology was appropriate, (5) there was loss to follow-up or dropouts in the study process, the reasons were explained, and the study utilized an intention-to-treat analysis methodology. One point was awarded for "Yes" and zero points for "No," with a total score of 5 points. Studies with 2 points were considered low-quality, while those with a score beyond 2 were considered high-quality.

Cochrane Reviewer's Handbook 4.2.5 edition was adopted for quality assessment, including whether (1) the study was a randomized trial; (2) allocation concealment was present; (3) blinding was utilized; (4) outcome data were complete; (5) there was selective reporting of results; (6) there were other biases.

2.4. Data extraction

Two researchers reviewed the literature independently, initially screening whether the studies were case-control or cohort studies and the data were complete. Based on the requirements, studies meeting inclusion criteria were selected, and each was assessed for its quality. Duplicate reports, studies of poor quality, and studies with too little reported confidence to be utilized were excluded. Data extraction was performed, and a database was created and verified. If a study report was incomplete, the authors were contacted for verification. Any studies deemed unusable were excluded from the study. Should there be different opinions, a third party was

consulted to resolve the issue. After full text acquisition, data extraction was performed, and the most recent study was selected in the case of duplicate reports. The data to be extracted were basic information about the literature (title, first author, publication year, author information, and source), characteristics of the study subjects (sample size, baseline comparability), the research methodologies employed in the literature, the study design, interventions for various groups, outcome evaluation indexes, and outcome data.

2.5. Statistical analysis

RevMan5.3 was employed. First, heterogeneity testing was performed with a significance level of $\alpha = 0.05$. At the same time, Peto's methodology was applied for heterogeneity analysis of the literature. When $I^2<50$ %, no heterogeneity existed in the literature, and a fixed-effect model (FEM) was employed for analysis. When $I^2>50$ %, heterogeneity existed in the literature, and a random-effect model (REM) was employed. For continuous data results, weighted mean differences (WMD) were utilized to represent results with the same units of measurement, and standardized mean differences (SMD) were utilized otherwise. For count data results, relative risks (RR) were utilized. All results were indicated using a 95 % confidence interval (CI). The difference was statistically significant with $P < 0.05$. A funnel plot was created, and the symmetry of funnel plot and the concentration of literature towards the centerline were utilized to assess publication bias. Sensitivity analysis was implemented to evaluate reliability and stability of results.

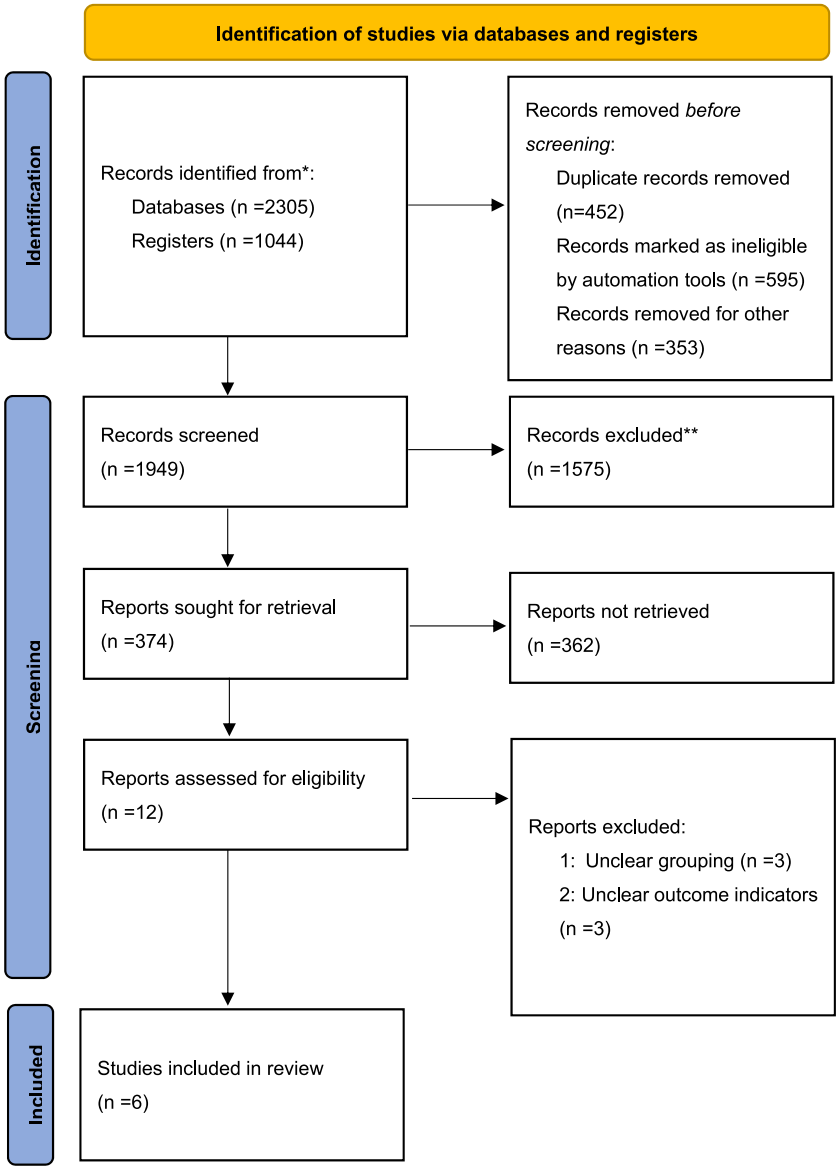

Fig. 1. Flowchart of the document search process.

3. Results

3.1. Search results and overview analysis

This study involved a search of a total of 3349 relevant literature sources, of which 1137 were retrieved from the Medline database, 1100 from the EMbase database, and 68 from the EBSCO database. A total of 1044 sources were manually searched. After inclusion and exclusion criteria were applied, 1400 sources were preliminarily excluded. A further 1575 sources were excluded based on their titles and abstracts, as they didn't meet inclusion criteria. After full text reading, due to the inability to extract data, 362 were excluded. Six sources [16–21] were ultimately included in the analysis, and the detailed screening process is presented in Fig. 1. Basic characteristics of patients and study indicators described in the literature are presented in Table 1.

3.2. Bias risk evaluation

In Figs. 2 and 3, based on the assessment, none of the six studies included in this analysis exhibited evidence of selection bias in terms of random sequence generation, incomplete outcome data, or reporting bias. The overall risk of bias for the included studies was found to be low.

3.3. Worsening of disease condition 24 weeks after treatment

Three studies analyzed the disease deterioration in pediatric patients after 24 weeks of treatment, and the results are presented in Fig. 4. Heterogeneity analysis showed $I^2 = 91$ %, $P < 0.00001$, so a REM was utilized for subsequent analysis. Comprehensive model analysis implied that OR was 0.10, with a 95 % CI of 0.03–0.41, Z = 3.24, $P = 0.001$. Hence, a drastic difference existed in disease deterioration between pediatric patients treated with omalizumab and those treated with other drugs at 24 weeks of treatment ($P < 0.05$). Fig. 5 shows a funnel plot analysis of disease deterioration in pediatric patients after 24 weeks of treatment. As presented in funnel plot, it was essentially symmetrical, and most data corresponded to points within 95 % CI, indicating inconsiderable publication bias.

3.4. Worsening of disease condition 52 weeks after treatment

Three studies were included to analyze the deterioration of the disease in children after treatment for 52 weeks (Fig. 6). The heterogeneity analysis showed $I^2 = 95$ %, $P < 0.00001$, thus a REM was employed. Comprehensive model analysis showed an OR of 0.27, with a 95 % CI of 0.09–0.83, Z = 2.28, and $P = 0.02$. This indicates that the difference in the deterioration of the disease between children treated with omalizumab and those treated with other drugs was marked ($P < 0.05$) after 52 weeks of treatment. Fig. 7 presents the analysis of the deterioration of the disease in children after treatment for 52 weeks by funnel plot. As presented in Fig. 7, funnel plot was generally symmetrical, and most data corresponded to points within 95 % CI, indicating that publication bias was effective.

3.5. Adverse event occurrence during treatment

Four articles were included in the analysis of adverse events in pediatric patients during treatment, as Fig. 8 presents. The heterogeneity analysis results showed $I^2 = 4$ %, $P = 0.35$, therefore a REM was employed for subsequent analysis. The comprehensive model analysis results implied that OR was 0.87, with a 95 % CI of 0.60–1.29, Z = 0.68, and $P = 0.49$. Hence, slight difference existed in the occurrence of adverse events in pediatric patients treated with omalizumab versus those treated with other drugs during treatment, with no statistical significance ($P > 0.05$). Fig. 9 is a funnel plot analysis of adverse events in pediatric patients during treatment, which was symmetric and most data points corresponded to 95 % CI, indicating effective publication bias.

4. Discussion

Allergic contact dermatitis (ACD) is the most complex and common skin disease in dermatology, caused by allergens through a hypersensitivity reaction. Its incidence is quite high, accounting for 50 % of all skin diseases. With the control of infectious diseases and

Table 1
Basic information.

First author	Publication year	Research group	Control group	Indexes
Lanier B	2009	421	207	Worsening rate of the disease (24 weeks, 52 weeks), adverse events
Kulus M	2010	159	76	Worsening rate of the disease (24 weeks, 52 weeks)
Busse WW	2011	208	211	Worsening rate of the disease (24 weeks, 52 weeks)
Milgrom H	2011	624	302	Adverse events
Kamin W	2010	113	106	Adverse events
Milgrom H	2001	225	109	Adverse events

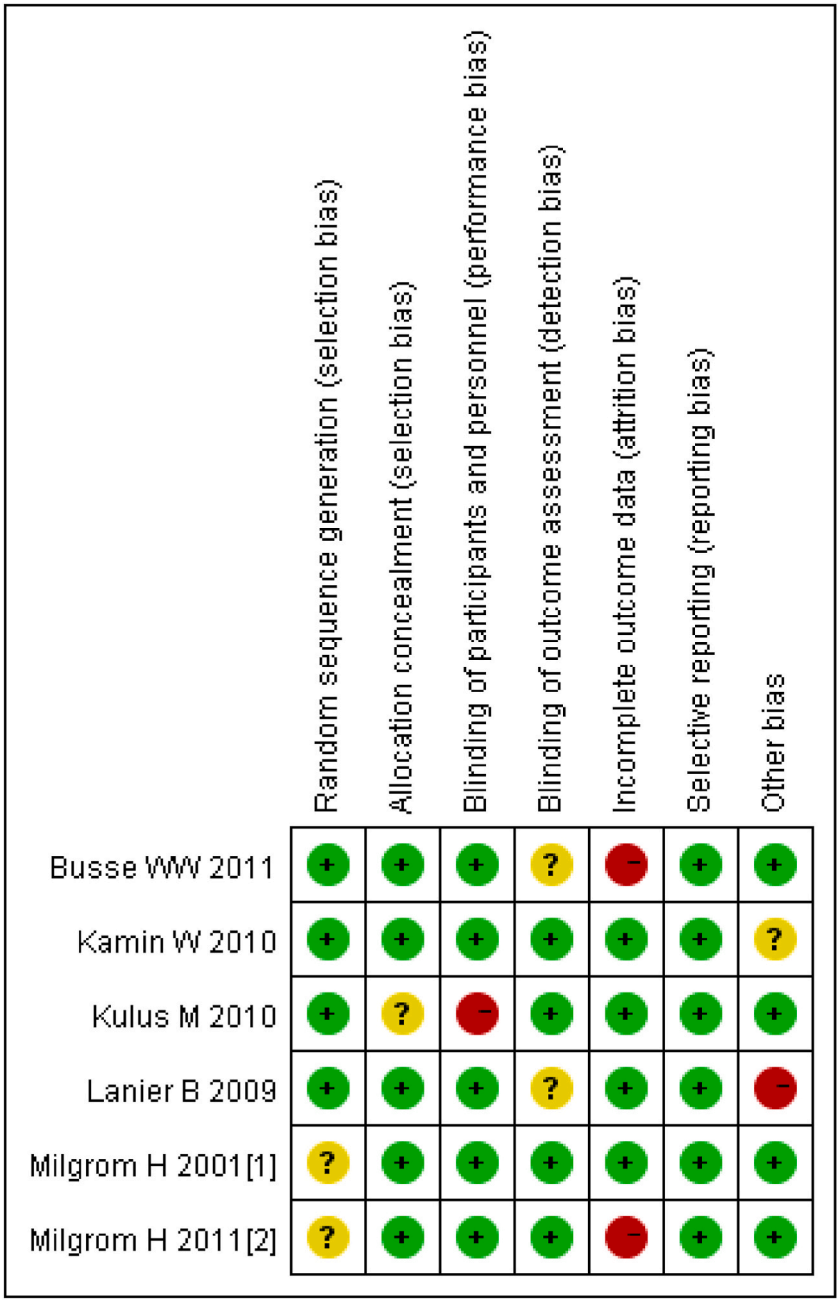

Fig. 2. Bias risk assessment.

the improvement of industrialization level, allergic diseases are showing an increasing trend in both China and globally [22,23]. ACD, also known as hypersensitivity or hyperreactivity, refers to a specific immune response characterized by physiological dysfunction or tissue damage when the body is exposed to certain antigens for the first time and then receives the same antigenic stimulation again. Omalizumab targets circulating free IgE and blocks its interaction with IgE receptors, thereby interrupting allergic cascade reaction [24,25]. Due to its unique composition, it meets all the requirements for clinical use, it seems to be able to reduce allergic inflammation by inhibiting IgE binding to its receptors, leading to a decrease in mediator release. In this study, relevant literature on the adoption of omalizumab in pediatric allergic diseases was collected and its adoption effect was explored through a meta-analysis.

The results implied that at 24 and 52 weeks after treatment, the number of children with worsened condition in the experimental group was notably inferior to controls ($P < 0.05$), and incidence of adverse reactions differed drastically between groups during the treatment period ($P > 0.05$). Chen et al. (2020) [26] applied omalizumab to treat severe atopic dermatitis in children and found that it could remarkably reduce severity of atopic dermatitis and enhance the quality of life of pediatric patients with atopic and severe

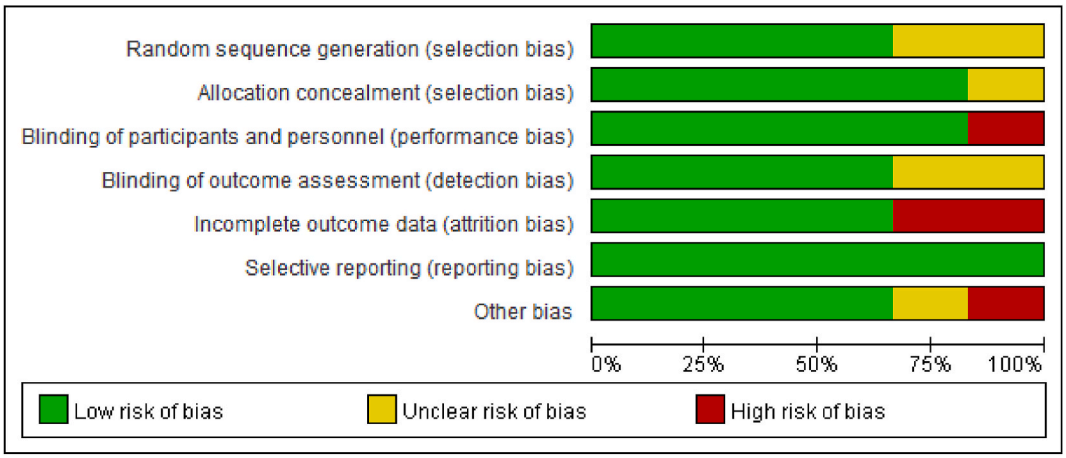

Fig. 3. Bar chart of bias risk assessment.

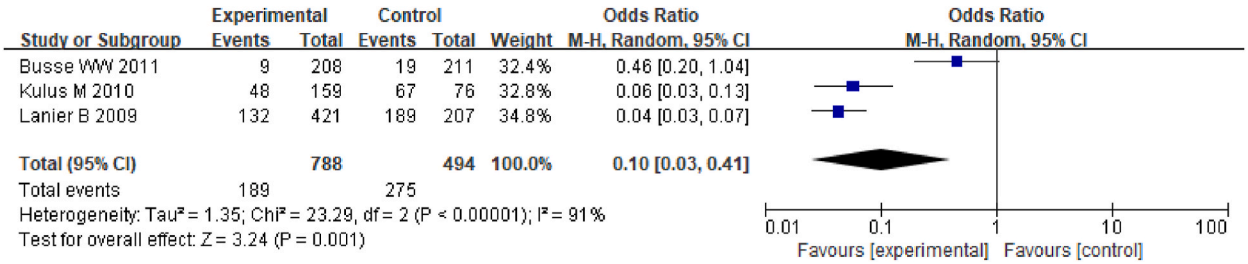

Fig. 4. Forest plot analysis of disease worsening 24 weeks after treatment.

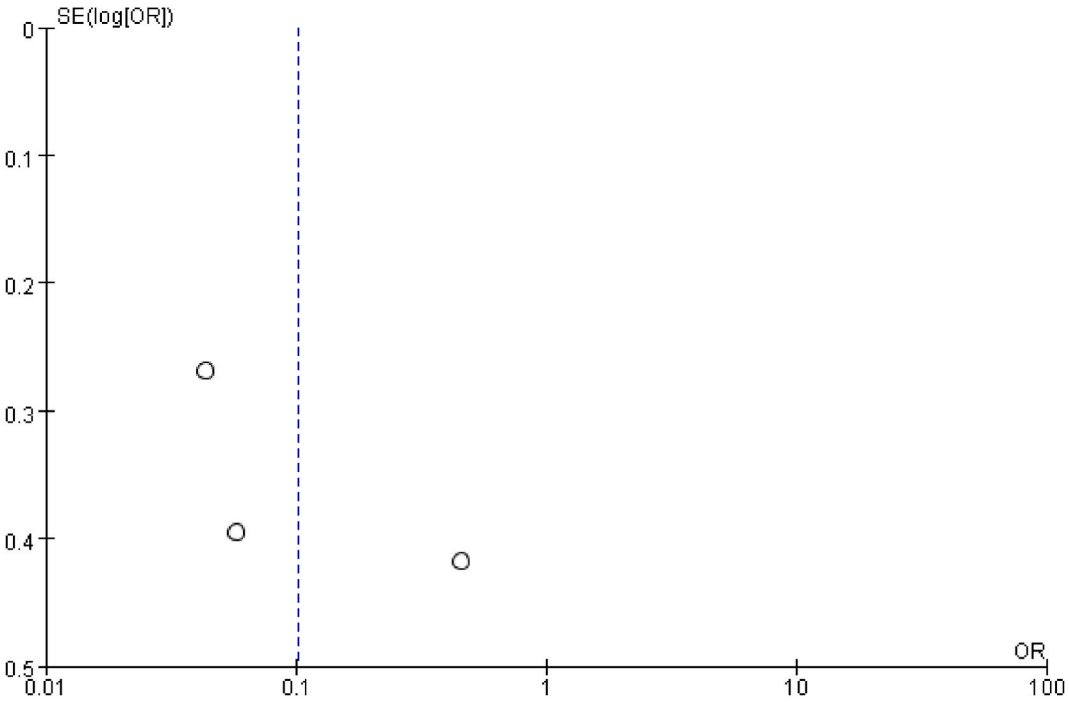

Fig. 5. Funnel plot analysis of disease worsening 24 weeks after treatment.

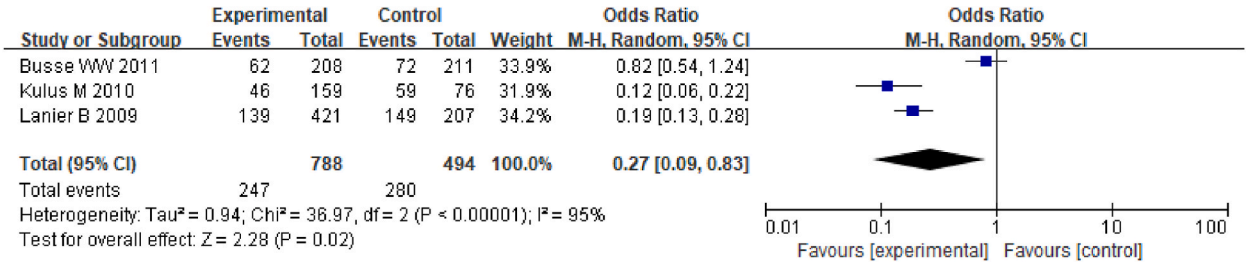

Fig. 6. Forest plot analysis of disease worsening 52 weeks after treatment.

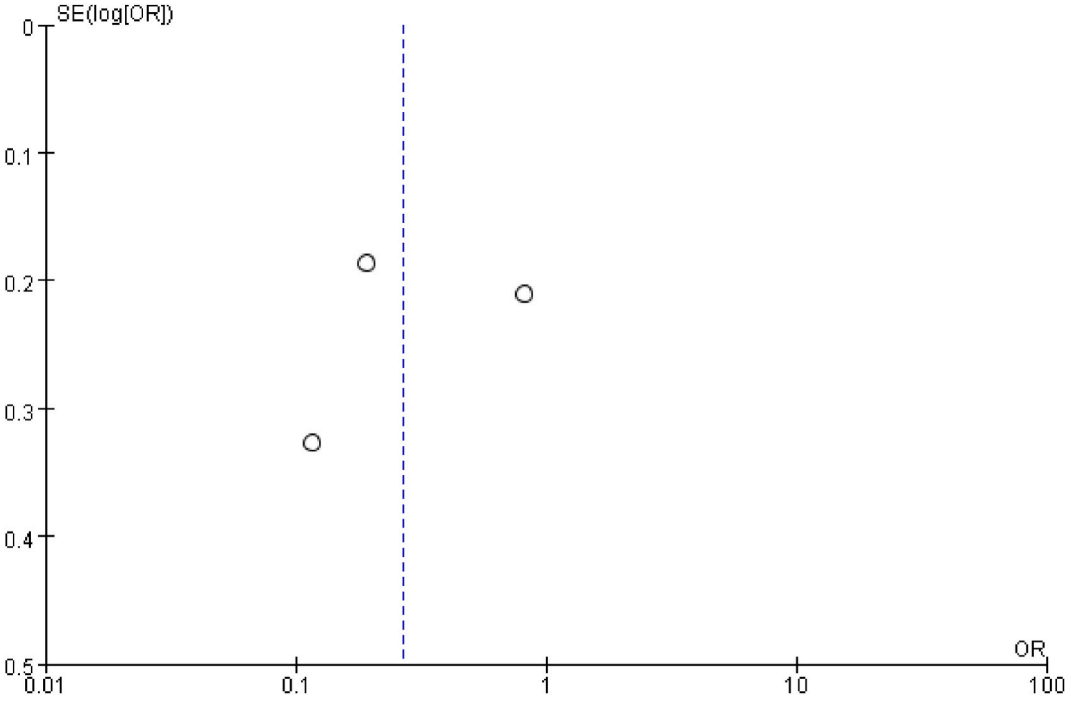

Fig. 7. Funnel plot analysis of disease worsening 52 weeks after treatment.

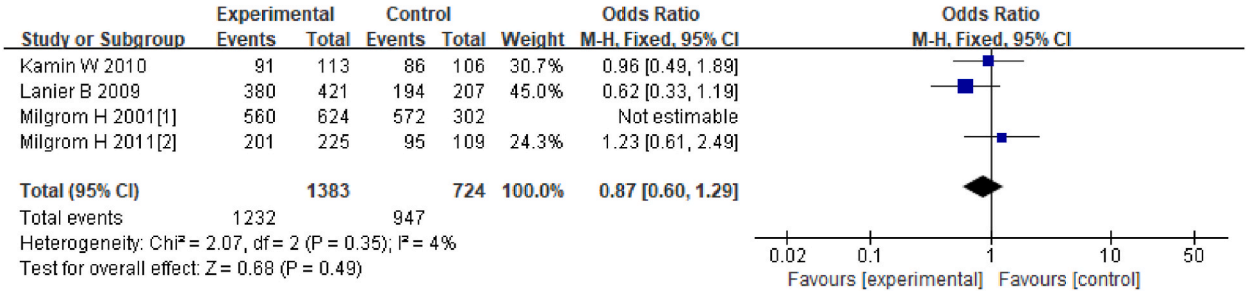

Fig. 8. Forest plot analysis of adverse event occurrence during treatment.

eczema. Scholars also evaluated the effect of omalizumab on allergic rhinitis through indicators such as quality of life, reduction of rescue drug use, and clinical improvement of adverse events. The results implied that compared with conventional treatment, omalizumab had better efficacy, and no considerable difference in adverse events was observed between omalizumab and placebo [27]. Another study applied omalizumab to treat severe allergic asthma and food allergy in patients who failed to respond to standard treatment [28]. Although it was not effective in controlling eosinophilic esophagitis, it could effectively control the symptoms of allergic asthma, allergic rhinitis, and sinusitis, and help patients with severe food allergies to undergo oral desensitization. These

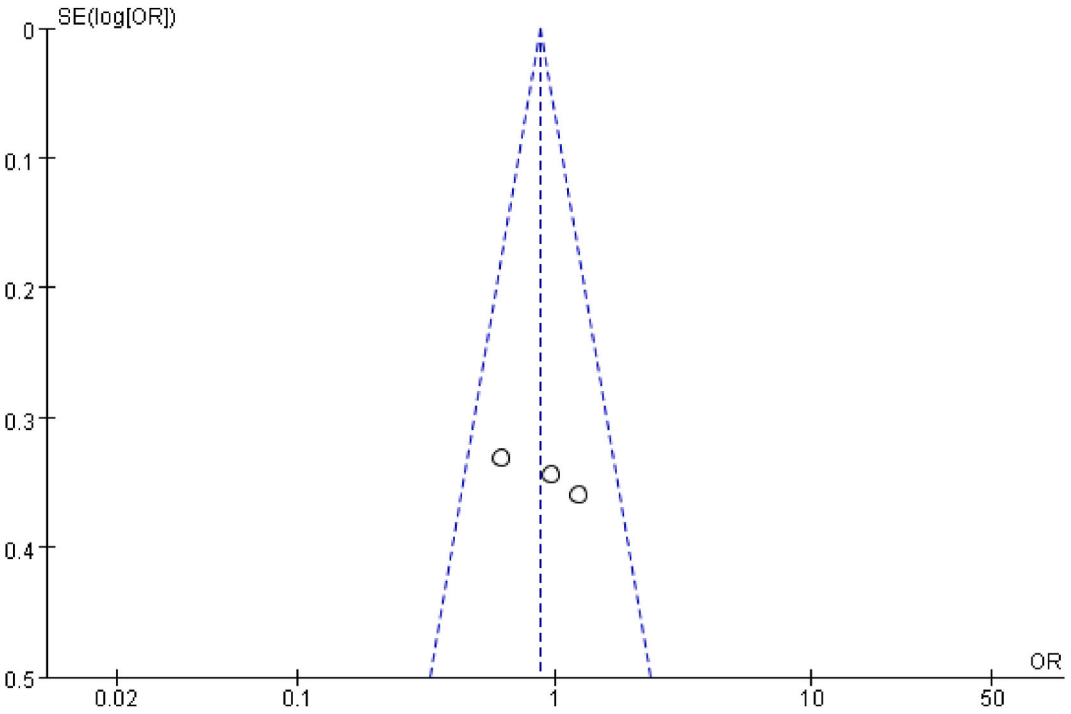

Fig. 9. Funnel plot analysis of adverse event occurrence during treatment.

findings are in line with the results of our study, indicating that omalizumab has good anti-allergic effects and good safety, and has adoption value.

Overall, this study integrated the results of multiple independent studies through meta-analysis to obtain more reliable and comprehensive conclusions, enhancing the reliability and practicality of the research findings, thus bearing significant implications for guiding clinical practice and future research. However, there is currently limited research on the application of omalizumab in pediatric allergic diseases, with most studies focusing on allergic asthma and rhinitis, which may introduce some bias into the results. Additionally, due to copyright restrictions, only English literature was included in this study, which imposes certain limitations on the research findings. Therefore, future studies need to be further improved to comprehensively analyze the efficacy of omalizumab in pediatric allergic diseases by incorporating more clinical data. Furthermore, the long-term prognosis of children during treatment was not mentioned in the research findings, which warrants further attention. Future research can expand the inclusion of literature, including literature in multiple languages, to reduce bias. Moreover, longer follow-up periods can be considered to evaluate the long-term effects of omalizumab treatment. Additionally, more clinical trials can be conducted to further validate the efficacy and safety of omalizumab. Finally, researchers can explore the combination of omalizumab with other treatment methods to improve treatment effectiveness.

5. Conclusion

Compared to conventional treatment, omalizumab can effectively alleviate allergic clinical symptoms in children, delay the progression of the disease, and has fewer adverse reactions and high safety, with adoption value. Nevertheless, due to the variety of childhood hypersensitivity diseases and the limited research on the adoption of omalizumab in childhood hypersensitivity diseases, which are mostly focused on allergic asthma and rhinitis, the results of this study have certain limitations. In the future, it is necessary to further improve and conduct a comprehensive analysis of the adoption effect of omalizumab in childhood hypersensitivity diseases through more clinical data.

Moral statement

This study did not require review and/or approval from the ethics committee, as it did not involve clinical or animal trials.

Data availability statement

Data not stored in public storage. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CRediT authorship contribution statement

Baihua Xu: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation. **Lingqun Tang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Data curation. **Wenzhen Huang:** Writing – review & editing, Visualization, Supervision, Resources, Investigation. **Shubin Xie:** Writing – review & editing, Validation, Formal analysis. **Jiaxin Ye:** Writing – review & editing, Formal analysis. **Guiping Luo:** Writing – review & editing, Writing – original draft, Project administration, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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