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Effectiveness of biologics for patients with severe asthma: study protocol for an umbrella review of systematic reviews and meta-analyses

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ABSTRACT

Introduction Many systematic reviews and meta-analyses (SRs/MAs) have evaluated the efficacy of biologic therapies for severe asthma. However, the overall quality of these SRs/MAs is unclear, which may influence the selection of biologics and lead to misleading clinical decisions. This umbrella review aims to objectively evaluate the overall quality of these SRs/MAs and reassess the efficacy of biologic therapies for severe asthma. Thus, this study will provide reliable evidence for clinical practice.

Methods and analysis A systematic search will be performed in PubMed, Embase, Cochrane Library, Web of Science, Scopus and conference abstracts up to 1 March 2025. Literature screening and data extraction will be conducted according to predefined inclusion and exclusion criteria. We will evaluate the reporting quality, methodological quality and evidence quality of these SRs/MAs using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, PRISMA for Network Meta-Analysis 2015 checklist, A MeaSurement Tool to Assess Systematic Reviews 2, Cochrane Risk of Bias 1.0 and Grading of Recommendations Assessment, Development and Evaluation system. Additionally, the re-analysis of outcomes will be performed using R software (V.4.3.3).

Ethics and dissemination Since this umbrella review will use publicly available data, ethics approval is not required. The results of this study will be disseminated through publication in a peer-reviewed journal.

PROSPERO registration number CRD42024607393.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first umbrella review that evaluates the efficacy of biologic therapies for patients with severe asthma.
⇒ This umbrella review will objectively evaluate the overall quality of eligible systematic reviews and meta-analyses.
⇒ Only articles in English will be included in this study, which may result in the exclusion of potentially relevant studies published in other languages.
⇒ Potential subjective bias may influence the evaluation of literature quality.

INTRODUCTION

Asthma is a prevalent chronic respiratory disease characterised by airway inflammation and airway hyper-responsiveness. It often presents with recurrent wheezing, shortness of breath, chest tightness, cough and other symptoms.[1] Asthma is a serious global health problem, affecting about 300 million people worldwide and causing about 250 000 deaths annually.[2] Additionally, and more importantly, patients with severe asthma have more significant symptoms, more frequent exacerbations and more serious adverse effects of medications, which can interfere with patients' daily lives, sleep and physical activity.[3] A Dutch study reported that about 3.7% of people with asthma suffer from severe asthma.[4] Furthermore, severe asthma is associated with higher healthcare expenditures. A Canadian study demonstrated that severe asthma accounts for over 60% of total asthma-related costs.[5]

Severe asthma refers to patients who remain uncontrolled despite adhering to maximal optimised high-dose inhaled corticosteroids (ICS)/long-acting beta-agonists (LABA) treatment and management of associated factors, or who worsen when high-dose treatment is decreased.[6] For these patients, add-on therapies, mainly emerging biologics, are needed to provide new hope for the treatment of severe asthma. Biologics can modulate the immuno-inflammatory cascade in the pathological course of severe asthma by precisely targeting inflammatory cytokines.[6] Biologics for severe asthma mainly include anti-immunoglobulin E (anti-IgE) treatment (eg, omalizumab), anti-interleukin-5/5Rα (anti-IL-5/5Rα) treatment (eg, mepolizumab, reslizumab, benralizumab), anti-interleukin-4Rα (anti-IL-4Rα) treatment (eg, dupilumab) and anti-thymic stromal lymphopoietin (anti-TSLP) treatment (eg,

tezepelumab). In previous studies, biologics have been shown to be beneficial for severe asthma, as they can reduce the frequency of acute exacerbations and hospitalisations, improve lung function and quality of life and decrease reliance on systemic corticosteroids.[7–9]

Recently, numerous systematic reviews and meta-analyses (SRs/MAs) have demonstrated the efficacy of biologics for severe asthma. However, these SRs/MAs also highlighted potential limitations. The reliability of the results may be affected by the heterogeneity among studies and other risks of bias. The methodological, reporting and evidence quality of these SRs/MAs remains unclear. The umbrella review can evaluate the overall quality of relevant SRs/MAs in detail, thereby providing high-quality evidence for clinical practice. To date, no umbrella reviews have been published on this topic, underscoring the need for this study to synthesise existing evidence.

In this umbrella review, the reporting, methodological and evidence quality of relevant SRs/MAs will be evaluated using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement, PRISMA for Network Meta-Analysis (PRISMA-NMA) 2015 checklist, A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) 2, Cochrane Risk of Bias 1.0 and Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. Additionally, we will re-evaluate the efficacy of biologics for patients with severe asthma. Ultimately, this study aims to provide evidence-based medical analysis for the use of biologics in severe asthma.

METHODS AND ANALYSIS

Design and registration

This protocol was registered in PROSPERO (registration number: CRD42024607393). The initial version was registered on 29 October 2024. It will be reported according to the PRISMA Protocol (PRISMA-P) 2015 statement.[10] The detailed PRISMA-P 2015 checklist can be found in online supplemental file 1. This study commenced on 15 November 2024 and is expected to be completed by 31 May 2025.

Inclusion criteria

Types of participants

This umbrella review will consider SRs/MAs that focus on participants aged ≥12 years with severe asthma. While the PROSPERO registration included participants aged ≥6 years, the final analysis will be restricted to ≥12 years due to insufficient high-quality evidence in younger populations. This adjustment ensures consistency with clinical practice and avoids bias from limited data. The criteria for severe asthma will refer to the 2024 Global Initiative for Asthma.[6]

Types of interventions

All participants with severe asthma received routine therapy with high-dose ICS-LABA combinations. Biologic therapies were administered strictly as add-on treatments to this background regimen. The investigated biologics included anti-IgE treatment (omalizumab), anti-IL-5/5Rα treatment (mepolizumab, reslizumab, benralizumab), anti-IL-4Rα treatment (dupilumab) and anti-TSLP treatment (tezepelumab).[6]

Types of comparisons

The control group will be given routine therapy or corresponding placebos.

Types of outcomes

The literature is required to report one or more of the following outcomes: annualised asthma exacerbation rate, the change from baseline in oral corticosteroids dosage, the change from baseline in pre-bronchodilator forced expiratory volume in 1 s, asthma control questionnaire, asthma control test, asthma quality of life questionnaire, number of hospitalisations due to asthma, blood eosinophil count and fractional exhaled nitric oxide (FeNO) levels.

Moreover, we will collect information regarding adverse events and serious adverse events caused by biologic therapy. Thus, we can evaluate the safety of biologics in patients with asthma.

Types of studies

This study will include eligible SRs/MAs of randomised controlled trials for analysis. Notably, we will also include articles on indirect treatment comparisons (ITCs) in our umbrella review, such as network meta-analyses (NMAs).

Exclusion criteria

Studies meeting any of the following criteria will be excluded: (1) articles for which the full text is not available, (2) articles without available data, (3) Duplicate or retracted studies and (4) articles in a language other than English.

Search strategy

Two authors (QX and BX) will independently carry out the retrieval of literature. PubMed, Embase, Cochrane Library, Web of Science and Scopus databases will be searched for literature. Conference abstracts from the American Thoracic Society International Conference, the European Respiratory Society International Congress, the CHEST Annual Meeting (American College of Chest Physicians) and the Asia Pacific Society of Respirology Congress will also be searched. The search will cover the period from the inception of each database to 1 March 2025. The search terms used include: ‘Mepolizumab’, ‘Reslizumab’, ‘Benralizumab’, ‘Omalizumab’, ‘Dupilumab’, ‘Tezepelumab’, ‘Asthma’, ‘systematic review’, ‘meta-analysis’ and ‘indirect treatment comparison’. The search strategy used in the PubMed database is listed in table 1. The full search strategy is provided in online supplemental file 2.

Table 1 Search strategy in PubMed

No	Search terms
#1	((((((((((Mepolizumab[MeSH Terms]) OR (Mepolizumab[Title/Abstract]) OR (SB-240563[Title/Abstract])) OR (SB240563[Title/Abstract])) OR (Nucala[Title/Abstract])) OR (Bosatria[Title/Abstract])) OR ((((((((((Reslizumab[MeSH Terms]) OR (Reslizumab[Title/Abstract]) OR (Cinqair[Title/Abstract])) OR (SCH-55700[Title/Abstract])) OR (SCH 55700[Title/Abstract])) OR (SCH55700[Title/Abstract])) OR (DCP-835[Title/Abstract])) OR (DCP 835[Title/Abstract])) OR (DCP835[Title/Abstract])) OR (CEP-38072[Title/Abstract])) OR (CEP38072[Title/Abstract]))) OR (((((Benralizumab[MeSH Terms]) OR (Benralizumab[Title/Abstract]) OR (MEDI-563[Title/Abstract])) OR (MEDI 563[Title/Abstract])) OR (Fasenra[Title/Abstract])) OR (BIW-8405[Title/Abstract]))) OR ((Omalizumab[MeSH Terms]) OR (Xolair[Title/Abstract]))) OR ((((((Dupilumab[MeSH Terms]) OR (Dupilumab[Title/Abstract]) OR (SAR231893[Title/Abstract])) OR (SAR-231893[Title/Abstract])) OR (REGN668[Title/Abstract])) OR (REGN-668[Title/Abstract])) OR (Dupixent[Title/Abstract]))) OR (((((((Tezepelumab[MeSH Terms]) OR (Tezepelumab[Title/Abstract]) OR (MEDI-9929[Title/Abstract])) OR (MEDI9929[Title/Abstract])) OR (MEDI-19929[Title/Abstract])) OR (AMG-157[Title/Abstract])) OR (tezspire[Title/Abstract])) OR (tezepelumab-ekko[Title/Abstract]))))
#2	((((Asthma[MeSH Terms]) OR (Asthmas[Title/Abstract])) OR (Asthma, Bronchial[Title/Abstract])) OR (Bronchial Asthma[Title/Abstract])))
#3	((((((((((((Meta-Analysis as Topic[MeSH Terms]) OR (Meta Analysis[Publication Type])) OR (meta analysis[Title/Abstract])) OR (meta analyses[Title/Abstract])) OR (meta-analysis[Title/Abstract])) OR (meta-analyses[Title/Abstract])) OR (data pooling[Title/Abstract])) OR (data poolings[Title/Abstract])) OR (clinical trial overview[Title/Abstract])) OR (clinical trial overviews[Title/Abstract])) OR (systematic review[Title/Abstract])) OR (systematic reviews[Title/Abstract])) OR (indirect treatment comparison [Title/Abstract]))
#4	#1 AND #2 AND #3

Study selection

After removal of duplicate studies, two reviewers (QX and YH) will individually examine the titles and abstracts of eligible articles that meet the inclusion and exclusion criteria and exclude irrelevant studies. EndNote (V.20) software will be used to generate citations and remove duplicate articles.[11] Then, two authors (QX and YH) will independently review the full texts of remaining articles and determine the final studies to be included in the umbrella review. All disagreements will be resolved by the third independent author (MW). The process of selecting studies is illustrated in figure 1.

To prevent the double counting of data, we will implement a systematic approach to manage overlapping primary studies across included SRs/MAs. Initially, we will create a comprehensive inventory of all primary studies and identify any overlaps. Then, we will exclude duplicate data to ensure that data from each primary study are included only once. Additionally, if multiple SRs/MAs include the same primary studies, the datasets may be merged. In the final umbrella review, we will report the methods used to handle overlapping primary studies.

Data extraction

Data extraction will be conducted by two researchers (BX and YH). We will extract information from eligible SRs/MAs. Extracted information from each SR/MA includes name of first author, year of publication, title of SR/MA, country, databases searched, number of clinical studies, sample sizes per group, disease duration, average age per group, gender ratio per group, type and dose of biologics, treatment duration, type of comparisons, blood eosinophil count, FeNO, IgE, sIgE levels, efficacy and safety outcomes, type of effect sizes, effect sizes for efficacy and safety outcomes, heterogeneity and publication bias. Any discrepancies will be resolved by discussion.

To enhance the depth and robustness of our analysis, first, we will extract GRADE ratings (eg, high, moderate, low or very low) for critical outcomes from SRs/MAs. Furthermore, we will also collect information on the methodological quality of these SRs/MAs using tools like AMSTAR 2, including the name and version of the assessment tool used, its core evaluation criteria or domains, assigned scores, and any conclusions drawn regarding the certainty of the evidence.

Quality assessment

All quality assessments will be conducted by two independent reviewers (QX and YH). Discrepancies will be resolved by consulting a third reviewer (MW). Before the quality assessment process, all reviewers will participate in a training session focused on the use of these quality assessment tools to enhance inter-rater agreement and minimise bias.

Reporting quality assessment

The reporting quality of the included SRs/MAs will be evaluated using the PRISMA 2020 statement.[12] It consists of 27 items and is scored as follows: a complete report is worth 1 point, a partial report is worth 0.5 points and an incomplete report is worth 0 points. If all required content is reported, the item will be classified as 'complete report'; if ≥50% of the reported content is reported with some key information missing, it will be classified as 'partial report'; if <50% of the reported content is reported or critical elements are missing, it will be classified as 'incomplete report'. The total score of the PRISMA statement is 27 points. In the final evaluation, a score of ≤15 indicates

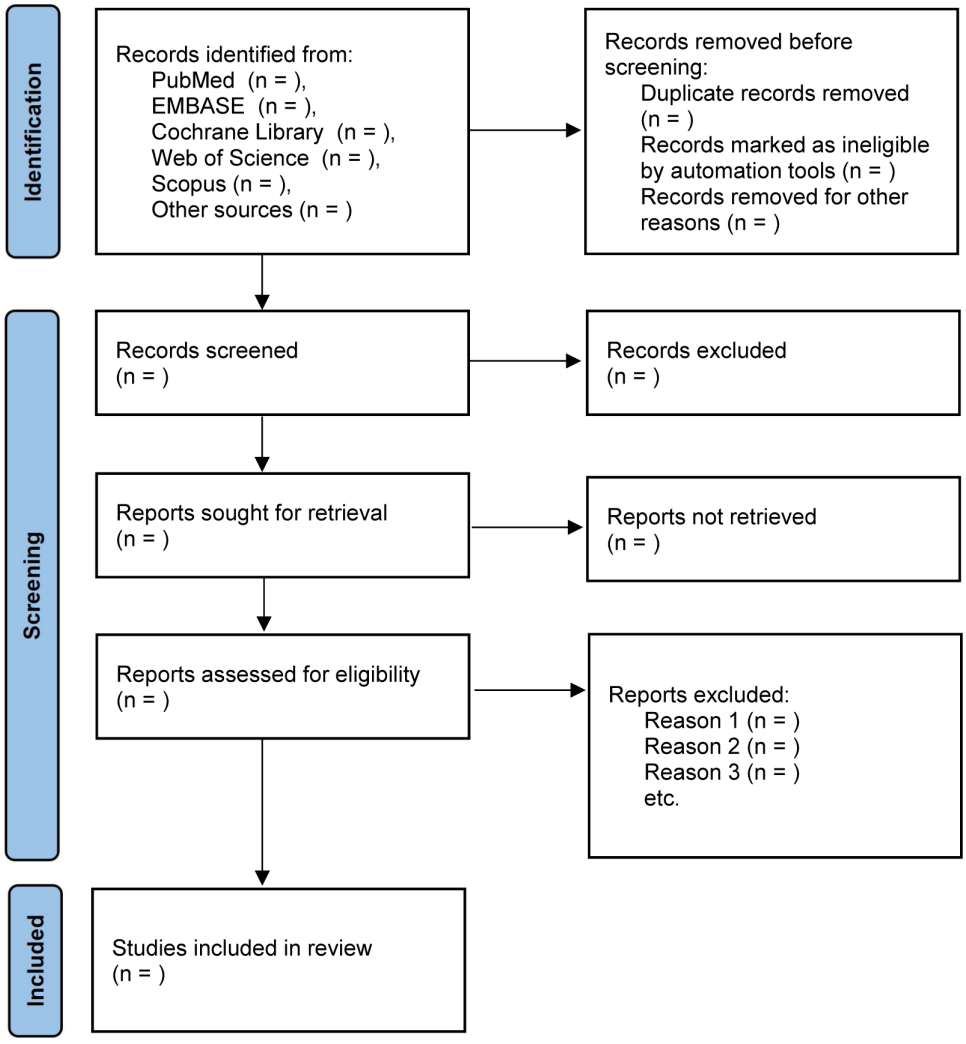

Figure 1 Flow chart diagram of study selection.

that the report has relatively serious information defects, a score of 15.5–21 indicates that the report has some defects, and a score of 21.5–27 indicates that the report is relatively complete.[13]

Additionally, the PRISMA-NMA 2015 checklist will be used to assess the reporting quality of the included ITCs.[14] It includes 32 items, and the total score is 32 points. Scoring follows the same criteria as the PRISMA 2020 statement. In the final evaluation, a score of ≤18 indicates that the report has relatively serious information defects, a score of 18.5–25 indicates that the report has some defects and a score of 25.5–32 indicates that the report is relatively complete.

Risk of bias (Methodological quality) assessment

In this umbrella review, we will assess the methodological quality of included SRs/MAs using the AMSTAR 2 tool.[15] It includes 16 items, with seven key items. The AMSTAR 2 development team recommended focusing on the methodological conditions of key items and determining the overall quality. Each item has the following options: yes, partial yes or no. The methodological quality of each SR/MA will be categorised as high, moderate, low, or critically low.

The methodological quality of ITCs will be assessed using the AMSTAR 2 tool, augmented with NMA-specific criteria from the International Society for Pharmacoeconomics and Outcomes Research, Academy of Managed Care Pharmacy, National Pharmaceutical Council checklist.[16] The four criteria include transitivity assessment, direct and indirect evidence consistency, model selection justification and cautious interpretation of rankings. Each item is rated yes, partial yes or no, with overall quality categorised as high, moderate, low, or critically low.

Furthermore, we will assess the risk of bias of primary studies through seven aspects: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias.[17] In our final review, we will report these assessments, discussing their potential impact on the overall conclusions.

Quality of evidence assessment

In terms of quality of evidence, we will apply the GRADE system to assess it.[18 19] It will be classified into four grades: high, moderate, low and very low. The upgrading factors for evidence quality include large effect size, residual confounding, dose-response relationship, and adequate sample size, while the degrading factors include study limitations, inconsistency, indirectness, publication bias and imprecision.

Management of duplicate reports

To systematically address duplicate publications, we will implement manual verification to identify potential duplicates based on overlapping titles, author affiliations, trial registration numbers and data characteristics. Confirmed duplicates will be resolved by prioritising the most recent publication to capture methodological updates. If publications are within 6 months of each other, the study with the larger sample size and more comprehensive data will be selected. All decisions will be reviewed independently by two researchers, and discrepancies will be resolved through consensus. The entire process will be thoroughly documented to ensure reproducibility.

Statistical analysis

All analyses will be conducted through the 'meta' package in R 4.3.3 software. Outcomes will be expressed as mean difference (MD) and risk ratio (RR) with corresponding 95% CIs. First, we will assess the heterogeneity of included studies by using the Cochran's Q test and I^2 statistics.[20] $p<0.1$ or $I^2>40\%$ indicates significant heterogeneity, and the random-effects model will be used.[21] Otherwise, we will choose the fixed-effects model. Then, we will calculate pooled MDs or RRs with 95% CIs for each outcome of different biologics. The results will be presented in the text, tables, and figures. $p<0.05$ indicates statistical significance.

Data from ITC and direct comparison articles will be analysed together. Sensitivity analysis will also be conducted to evaluate the impact of each study on overall results. When interpreting the results, evidence from both ITC and direct comparison articles will be considered to provide a more comprehensive efficacy assessment. Due to the uncertainty of ITC results, we will interpret the findings cautiously.

In addition, subgroup analysis will be conducted to explore the potential sources of heterogeneity. The subgroups will include population characteristics (age, baseline disease severity and blood eosinophil count) and intervention variables (types of biologics, dosage and treatment duration). The publication bias will be evaluated through funnel plots and Egger's test, which will only be performed when the number of studies exceeds 10 to ensure sufficient statistical power.

DISCUSSION

In recent years, many SRs/MAs have been published. However, concerns have been raised about the generalisability and validity of such analyses. Different study populations and types of original studies, combined with varying degrees of methodological flaws in SRs/MAs, may lead to misleading clinical decisions. Employing the latest evidence-based medicine analysis, the umbrella review based on SRs/MAs provides more robust and reliable evidence for clinical practice and compensates for the limitations of individual SRs/MAs.[22]

Asthma is a serious global health problem, and people with severe asthma have more severe symptoms, frequent exacerbations and significant medical economic burden.[23] In previous SRs/MAs, biologics have demonstrated promising efficacy and safety and are considered a promising treatment for severe asthma.[24–26] Nevertheless, the overall quality of these SRs/MAs is still unclear, prompting the need for an umbrella review. The findings of this review will further strengthen the evidence-based medical basis for the application of biologics in severe asthma and provide guidance for clinical practice.

Sample size is a critical factor influencing the reliability of SRs/MAs. Adequate sample size enhances the precision of effect estimates and reduces the risk of bias, both of which are essential for high-quality evidence. Therefore, incorporating sample size as an additional factor in the GRADE system can provide a more comprehensive evaluation of the quality of evidence. In this study, we will pay special attention to the sample size of included SRs/MAs to ensure the robustness of our findings.

However, this study has some limitations. First, we will include only articles in English and exclude studies published in other languages. As most databases and literature resources are in English, language restrictions help ensure data accuracy and consistency, thereby facilitating precise data extraction and analysis. Second, some subjective factors may affect the evaluation of literature quality.

Patient and public involvement

Patients and the public will not participate in the design and implementation of the study. The research results will be made available to the patient and public.

ETHICS AND DISSEMINATION

Since this study will use publicly available data, ethics approval is not required. We will disseminate the results of this review through a peer-reviewed journal.

Contributors QX designed the study, submitted the registration to PROSPERO and wrote the manuscript. QX and BX completed the search strategy. QX and YH revised the language. MW is responsible for directing the overall study. MW is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer-reviewed.

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