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Cost-effectiveness and efficacy analysis of biosimilar drugs for lung diseases: a systematic review

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Abstract

Purpose – Cost-effectiveness analysis is an organized method that aids in evaluating and examining the economic aspects and health results linked to different medical procedures. Efficacy analysis considers how effectively a treatment achieves the intended outcome when tested under perfect and controlled conditions. Nowadays, there is a noticeable trend towards using biologics and biosimilar medicines. Specifically, biosimilars are seen as a cheaper alternative to treat long-term health issues traditionally linked with significant medical expenses. A key area for the use of biosimilars is lung diseases, with a fast-growing number of studies on their applications.

Design/methodology/approach – Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a systematic review has been conducted. Bibliometric data were collected from the Dimensions database in March 2025. The keywords selected are "biological," "drugs," "biosimilar," "lung," "diseases," "cost," "effectiveness," "efficacy" and "analysis." The timespan considered goes from 2004 to 2024.

Findings – Of the 2,852 papers retrieved based on our inclusion criteria, only 28 articles published in peer-reviewed journals were considered relevant. Biosimilar drugs are more cost-effective and efficacious than reference drugs, with improvements in asthma control and quality-adjusted life years, though at higher costs in certain cases. No specific conditions alter their economic benefits, except when combined with chemotherapy. Moreover, they are used in various lung diseases, including different types of lung carcinoma and severe allergic asthma. Robust models were used for the cost-effectiveness and efficacy analysis.

Originality/value – The reported outcomes serve as a tool for researchers and policymakers aiming to explore the integration of these new drugs into the healthcare system. From a policy perspective, obtaining a clearer insight into the current landscape enables policymakers to allocate additional funding towards the adoption of cost-effective and efficacious biosimilars in specific areas, improving patient benefit and potentially lowering public healthcare expenditures.

Keywords Cost-effectiveness analysis, Efficacy, Lung diseases, Biosimilar drugs, Systematic literature review

Paper type Literature review

1. Introduction

Cost-effectiveness analysis (CEA) is an intricate and systematic approach that facilitates the assessment and scrutiny of both the financial implications and health outcomes associated with various medical activities, involving a comparative evaluation of multiple potential interventions or the introduction of one or more novel interventions against the existing standard practices, often referred to as the "status quo." Essentially, CEA, a method used in economic evaluation, acts as a tool to provide understanding of the health advantages and

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financial costs linked to a medical intervention in comparison to an alternative approach or the prevailing standard of care (e.g. Garber and Phelps, 1997; Drummond *et al*., 2001; Eichler *et al*., 2004; Bowrin *et al*., 2019; Lu *et al*., 2021).

Not considering costs, efficacy analysis describes how effectively a treatment or intervention achieves the intended outcome when tested under perfect and controlled conditions, as in an experimental environment and, like those in a clinical trial (e.g. Kandi and Vadakedath, 2023; Singh *et al*., 2023; Hartman, 2024).

CEA has become a key tool for health technology assessment organizations worldwide, guiding health intervention decisions. It helps determine market entry, pricing strategies, and formulary inclusion, ensuring efficient resource allocation in healthcare (Philips *et al*., 2006; Yang *et al*., 2008; Clement *et al*., 2009; Ciani and Jommi, 2014; Dakin *et al*., 2015; Jönsson, 2015; Lu *et al*., 2021).

In this sense, the pharmaceutical industry is shifting towards biologics and biosimilars, which are derived from living organisms using biotechnological processes. These methods employ bacteria, yeast, and human cells to alter DNA for medical treatments and diagnostics. Unlike biologics, traditional chemical medicines are synthesized through chemical agents, thus producing identical products (Young, 1986; Nagle *et al*., 2003; Simoens, 2011). Biosimilars offer a cost-effective solution for treating chronic conditions like diabetes, cancer, respiratory disorders, and closely resemble an original biological drug that was previously patented and authorized for distribution, commonly referred to as the "reference", "originator", or "innovator" drug (e.g. Simoens, 2011; Rathore and Bhargava, 2020).

Developing biological drugs is an expensive and lengthy process, often requiring hundreds of millions of euros and around a decade of research. To recover these costs, patents typically last about twenty years, allowing the innovating company to secure profits. Once patents expire, biosimilars, produced by companies that did not bear initial research expenses, can enter the market at lower costs. This price difference is crucial, as biosimilars offer significant financial savings (Rathore and Bhargava, 2020; Safardoust *et al*., 2025). However, their cost-effectiveness depends on their ability to replicate the therapeutic effects of the original biopharmaceutical (Simoens, 2011).

Biosimilars differ from traditional generic drugs in their production and approval processes. While generics are identical to their reference drugs and undergo simplified authorization, biosimilars are highly similar but not identical to the originator. Due to differences in manufacturing, biosimilars may exhibit slight variations in efficacy, immunogenicity, and safety (Liu *et al*., 2019; Safardoust *et al*., 2025). However, technological advancements occurred in the timespan (about 10–20 years) between the release of the biological drug and the biosimilar one can enhance their effectiveness (Simoens, 2011). As a result, biosimilars undergo more rigorous testing and approval procedures. Despite these differences, biosimilars demonstrate comparable bioactivity to their reference product, particularly in terms of safety and effectiveness (Simoens, 2011; García *et al*., 2020; Simoens *et al*., 2017).

Efficacy and safety analysis also plays an important role in the process of developing new drugs (Chan *et al*., 2022; Hartman, 2024). In particular, the introduction of efficacious biosimilars at prices lower than their reference counterparts presents a potential economic advantage for the community at large, contributes to the fiscal sustainability of healthcare systems, and facilitates patient access to novel treatments that have emerged from scientific advancements (Huang *et al*., 2020).

Biological and biosimilar drugs play a crucial role in treating pulmonary diseases, which impair lung function due to exposure to airborne pollutants, tobacco smoke, and toxic gases (e.g. Luo *et al*., 2022). These conditions affect lung tissue, upper and lower airways, and blood vessels, ranging from common respiratory illnesses to rare and orphan diseases. The most common diseases include: acute and chronic infections (e.g. pneumonia, tuberculosis); neoplasms (lung cancer); chronic airway diseases (asthma, chronic obstructive pulmonary disease (COPD)–; interstitial and occupational diseases; pathology of the pulmonary vessels (e.g. pulmonary thromboembolism, pulmonary hypertension); obstructive sleep apnoea syndrome. Chronic

respiratory diseases are a leading cause of death and disability worldwide and healthcare costs for respiratory diseases represent an increasing burden on the economies at global level (OECD, 2016; Soriano *et al*., 2020; Safiri *et al*., 2022). COPD, a chronic condition marked by ongoing respiratory issues and restricted airflow, resulting from physical alterations in the airways and alveoli, typically triggered by protracted exposure to damaging elements or gases (Rycroft *et al*., 2012), is the third leading cause of death worldwide, resulting in 3.2 million deaths and accounting for the 81.7% of the total number of deaths from chronic respiratory diseases (Levine and Marciniuk, 2022). Although its incidence and mortality rates have steadily decreased over the past decade, lung cancer remains the primary cause of cancer-related deaths worldwide (Oliver, 2022). In detail, there are two main types of lung cancer: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), the latter divided into three subtypes: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. All types originate from epithelial tissue which covers the pulmonary structures. In particular, NSCLC represents the most frequent form, representing 85% of all lung cancers, and among these, Adenocarcinoma is the most common type of NSCLC, accounting for approximately 40% of lung cancers (Duma *et al*., 2019; Raad *et al*., 2024).

The aim of this article is to perform a systematic review on the literature about cost-effectiveness and efficacy analysis of biosimilar drugs for lung diseases, focusing on the quantitative models applied in this healthcare field.

In this sense, our contribution is innovative and differs from previous systematic literature on biosimilars. Among others, D'Angiolella *et al*. (2018), focusing on psoriatic arthritis, find that biologic therapies are cost-effective, despite their higher direct costs, since their improved efficacy and better patient management outweigh the expenses compared to conventional therapies; Liu *et al*. (2019) examines the economic impact of non-medical switching (NMS) from biologic originators to biosimilars, where medications are switched for reasons unrelated to a patient's health, finding that the overall economic impact of biosimilar NMS remains uncertain; Huang *et al*. (2020), focusing on Europe and the United States, finds evidence on the cost-effectiveness and affordability of oncology biosimilars; Li *et al*. (2021) focusing on economic evaluations of osteoporosis drug, including biosimilars, finds that some therapies were cost-effective or even dominant compared to standard practices such as oral bisphosphonates.

To the best of our knowledge, no other works have already performed a systematic review of the literature on the health economic evaluation of biosimilars for lung diseases. Therefore, the following research questions are investigated:

RQ1. Are biosimilar drugs cost-effective/efficacious compared to traditional and biological drugs?

RQ2. Under what circumstances, if any, do they have different levels of cost-effectiveness and efficacy?

RQ3. What are the main lung diseases in which biosimilar drugs are employed?

RQ4. What are the models used for cost-effectiveness and efficacy analysis in this field?

The remainder of the paper develops as follows. In section 2 we report a background of the models used in cost-effectiveness and efficacy analysis whereas section 3 describes materials and methods of our research. The results are provided in Section 4. Section 5 discusses findings, limitations, and avenues for further research while Section 6 presents final drawings and policy implications.

2. Background on modelling of CEA and efficacy analysis

The majority of healthcare practitioners perceive cost-effectiveness and efficacy analysis as the main reasons behind their favorable opinions on adopting biosimilars (Yang *et al*., 2022a).

Economic evaluations in healthcare help allocate limited public resources efficiently by assessing the net expenditure required to achieve health outcomes, such as increased life

expectancy or fatality prevention. The net cost of an intervention is calculated by subtracting avoided medical and productivity expenses from total costs. More effective interventions typically come with higher costs, leading to a positive net expenditure (Stinnett and Mullahy, 1998; Briggs, 2000; Philips *et al*., 2006). In CEA the results are obtained by calculating the cost-effectiveness ratio, which is the quotient of the net cost and the effectiveness of the intervention, namely the ratio of incremental costs or incremental cost-effectiveness ratio (ICER) (Dams *et al*., 2023). In practical terms, the net cost is divided by the variations in health outcomes culminating in the ICER, where negative ICER implies that an intervention that is more efficacious is also concurrently more cost-efficient. From a purely economic perspective, the preference would invariably be given to the intervention that demonstrates the lowest cost-effectiveness ratio, signifying the most prudent financial investment for the desired health outcome (Garber and Phelps, 1997).

Several economic models (e.g. Markov models, Monte Carlo Simulation models, Decision Tree models, Regression models, Discrete Event Simulation models-DES, Partitioned Survival Models-PSM) are used for performing CEA, being instrumental in assessing the effectiveness and relative costs of various treatment or intervention options, providing crucial insights for clinical decision-making and health policy (e.g. Fagery *et al*., 2023; Freitag *et al*., 2024; Raad *et al*., 2024; van Mossel *et al*., 2025).

Whereas effectiveness refers to its performance under real-world conditions, efficacy can be defined as the performance of an intervention under ideal and controlled circumstances (Hartman, 2024). Differently from CEA, efficacy analysis not consider costs and employs quantitative models to compare data from different treatment and determine whether the observed effects are statistically significant (e.g. Overall response rates (ORR), ANOVA, ANCOVA, survival analysis, regressions and correlations). To do this, the models are tailored to focus on the clinical aspects of a treatment, assessing its efficacy and safety for patients (e.g. Brugts *et al*., 2023; Ye *et al*., 2023; Han *et al*., 2024).

3. Materials and methods

The methodology employed in this work is a systematic literature review, providing a thorough summary of primary studies with clearly defined aims, materials, and methods. Unlike traditional reviews, it serves as an independent work with a transparent, replicable process, ensuring reliability and deeper inquiry into a specific topic (Greenhalgh, 1997; Snyder, 2019; Donthu *et al*., 2021; Finocchiaro Castro *et al*., 2024).

In contrast to systematic ones, narrative reviews present a more subjective interpretation of the literature, lacking the rigorous reporting of databases, selection criteria, and the detailed methodological transparency required for reproducibility (Rother, 2007; Snyder, 2019).

Systematic reviews, on the other hand, are rigorous and replicable, following predefined protocols from research question formulation to data synthesis, where clear search strategies and inclusion criteria ensure relevant, unbiased literature selection, enhancing the reliability and robustness of findings (e.g. Greenhalgh, 1997; Snyder, 2019; Finocchiaro Castro *et al*., 2024).

In this investigation, bibliographic information was sourced from Dimensions, a database established by Digital Science in 2018 (https://www.dimensions.ai/). In detail, Dimensions is an artificial intelligence-based database that enables access to the widest collection of bibliographic data in multidisciplinary research areas. This choice was made over other commonly referenced databases such as Web of Science, PubMed, EMBASE, Cochrane Library, which have been utilized in prior review studies within the field of biosimilars' economic evaluation (e.g. D'Angiolella *et al*., 2018; Liu *et al*., 2019; Huang *et al*., 2020; Li *et al*., 2021). The preference for Dimensions is attributed to its status as the most comprehensive, cutting-edge, and extensive repository of scientific data, surpassing traditional database such Web of Science and Scopus in the volume of documents it encompasses (Martín-Martín *et al*., 2021; Singh *et al*., 2021; Stahlschmidt and Stephen, 2022; Ferrara *et al*., 2023) and since Dimensions focuses more in the medical area rather than the

social sciences (Gusenbauer, 2022) [1]. Moreover, Liang *et al*. (2021), in choosing the most effective open-access bibliographic databases for conducting citation analysis in health field, reveals that Dimensions is the leading database surpassing the official National Institutes of Health–Open Citation Collection (NIH-OCC) dataset in terms of comprehensiveness.

The keywords used for the search string are applied to the areas "Title", "Abstract" and "Full Text". Indeed, only papers with the full text available are selected for this review. The employment of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines is deliberate, as it provides a structured and systematic approach for conducting comprehensive systematic reviews and meta-analyses. This methodology is renowned for its meticulousness and transparency, ensuring researchers that their work meets the highest standards of quality, thereby contributing meaningful and trustworthy findings to their respective fields (Page *et al*., 2021).

The parameters applied in retrieving the data, and described in Table 1, permitted us to focus the analysis specifically on the area of interest. Selection of keywords is of paramount importance in delineating the precise scope of the research area under investigation, permitting to effectively limit and focus the study to the most relevant and pertinent topics. The selected keywords are: "biological", "drugs", "biosimilar", "lung", "diseases", "cost", "effectiveness", "efficacy" and "analysis". The timespan considered is the 20-year period from 2004 to 2024, to analyse both seminal works and up-to-date studies that employs innovative models (Giddings *et al*., 2023).

To ensure transparency and provide a clear understanding of the data's currency, it is important to note that the information presented herein is drawn from a dynamic database that undergoes regular updates. This research dataset was sourced on March 15th 2025.

The documents considered are only articles published in peer-reviewed journals and written in English, excluding working papers, conference papers, notes, reports, and other forms of literature (see among others, Rycroft *et al.*, 2012; D'Angiolella *et al*., 2018; Li *et al*., 2021; Ferrara *et al*., 2023; Rathnayaka *et al*., 2023; Finocchiaro Castro *et al*., 2024). In total, 2,852 documents were retrieved for analysis and the most relevant ones are summarized in Section 4.

Figure 1 presents the number of publications for each year, showing a constant growing trend.

In Figure 2, the steps of the systematic review are illustrated in detail, according to the PRISMA guidelines (Page *et al*., 2021).

4. Results

4.1 Selection process and classification

Considering the 2,852 articles initially identified by the database Dimensions, thanks to the preliminary analysis of these documents, 47 were selected, as from an initial examination they appeared to be inherent to the topic covered (see Figure 2 PRISMA flow diagram).

These documents were downloaded and coded in progressive order as they appeared in the dataset. The studies concern the following countries: China, Germany, Greece, Iran, Italy, Japan, New Zealand, Spain, Taiwan, United Kingdom and USA.

Table 1. Parameters applied in retrieving data from dimensions database

Parameters	Selections
Document	Article
Language	English
Source	Journal
Keywords	"biological" and drugs" and "biosimilar" and "lung" and "diseases" and "cost" and "effectiveness" and "efficacy" and "analysis"
Time span	2004–2024

Note(s): Own elaboration

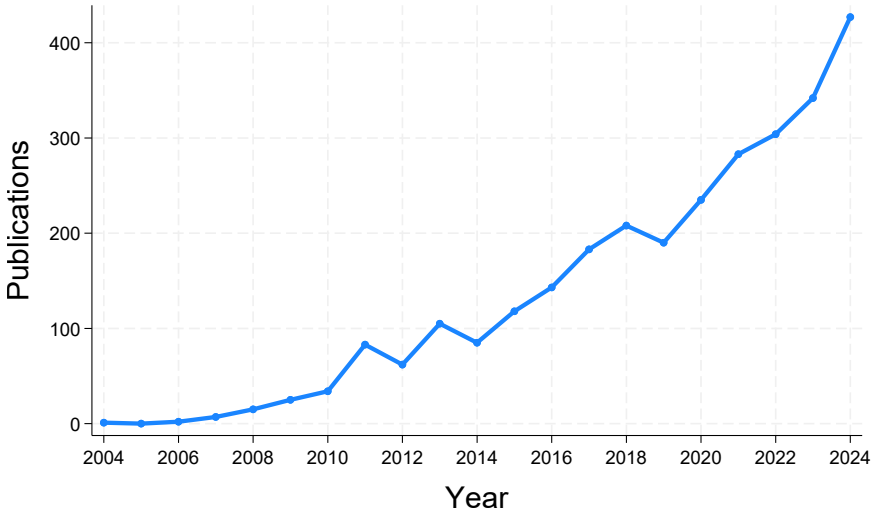

Figure 1. Publication trend by year (2004–2024). Note: Own elaboration from dimensions data with Stata 18 software

Subsequently, the 47 articles were subjected to a careful analysis from which it emerged that only 28 are relevant to our work as they provide important information to answer the identified research questions [2].

As a result, 19 articles were discarded because they did not address lung diseases (no. 7, 39, 43) or were limited to a model predicting exacerbation risk in patients with severe asthma (11) or only captured the relationship between virus and asthma development (21) or, in general, not making comparisons in terms of effectiveness and costs or efficacy between biosimilars and reference drugs (all the others). A summary of the discarded documents is reported in Table A1 in the online Appendix.

The 28 included articles have been classified according to the following applied methodologies:

(1) Literature review: 2, 4, 22, 23, 34, 38, 41;

(2) Randomized studies: 3, 6, 10, 15, 17, 18, 20; 40, 45, 46;

(3) Non-randomized studies: 16;

(4) Observational studies: 5, 13, 37, 42, 47;

(5) Model-based studies: 1, 8, 26, 35, 44.

In the online Appendix, Table A.2 presents their classification in relation to methodology, field of application, and presence of economic variables, while Table A.3 summarizes some information relating to the included papers, ordered according to the number with which they were coded.

4.1.1 Literature review. Several systematic reviews have assessed the efficacy, safety, and cost-effectiveness of biosimilars in oncology and respiratory care. Xiao *et al*. (2022) confirmed that bevacizumab biosimilars are comparable to the original drug in treating non-squamous NSCLC. Xu *et al*. (2022) found similar results for advanced NSCLC and metastatic colorectal cancer (mCRC). Malapelle and Rossi (2019) estimated that adding bevacizumab to chemotherapy (ChT) could significantly increase the cost-utility ratio, exceeding $500,000 per quality-adjusted life years (QALY). In adenocarcinoma, adding nintedanib to docetaxel was

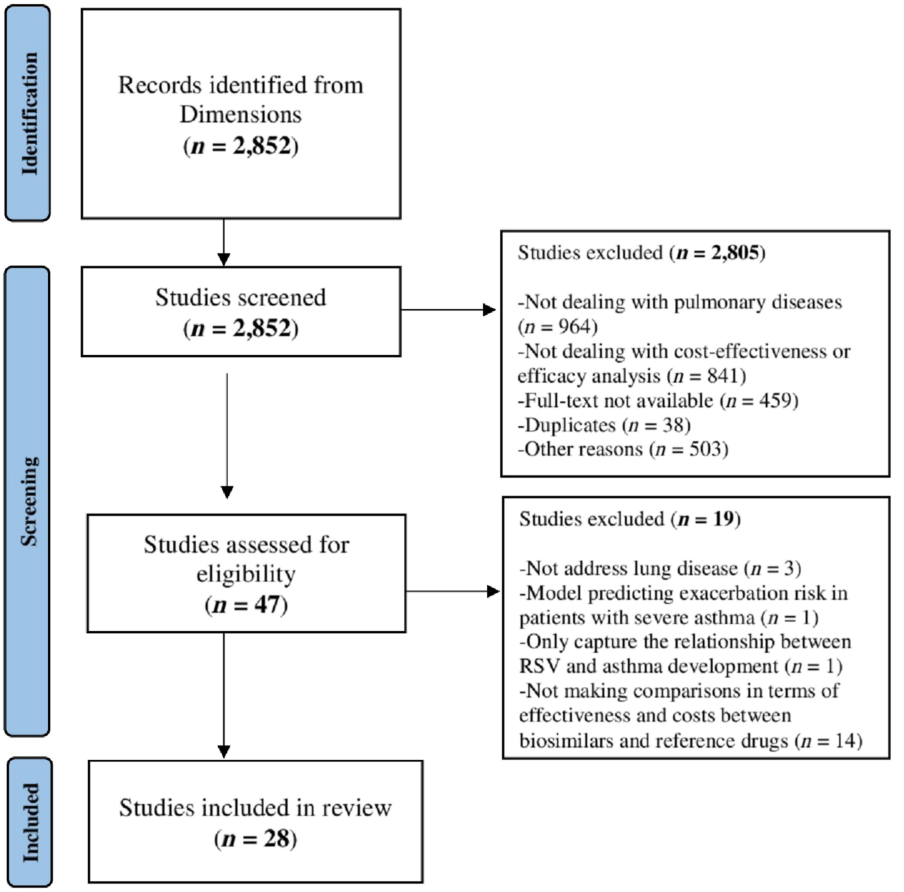

Figure 2. PRISMA flow diagram of the systematic literature review. Note: Own elaboration from Page *et al.* (2021)

estimated to have an ICER of €40,886. Kotoulas *et al.* (2022) highlighted omalizumab's benefits in improving asthma control and reducing exacerbation risks in severe allergic asthma. Moir (2023) highlights biosimilars as a cost-saving strategy in oncology, improving treatment accessibility for breast and lung cancer patients while reducing financial burdens on healthcare systems and individuals. Real-world evidence supports their effectiveness as affordable alternatives. Yang *et al.* (2022b) conducted a meta-analysis comparing bevacizumab biosimilars to Avastin in advanced non-squamous NSCLC. Extensive searches and trials found no significant differences in efficacy or safety between biosimilars and the original drug. Russo *et al.* (2017) reviewed bevacizumab use in advanced NSCLC, noting initial concerns over fatal haemorrhagic events. However, later studies confirmed its safety and tolerability, supporting its continued use in treatment.

4.1.2 Randomized studies. The randomized study by Syrigos *et al.* (2021) demonstrated the equivalence in efficacy and safety between the two drugs Bevacizumab Biosimilar FKB238 and the original Bevacizumab in patients with non-squamous cancer (NSCLC), reporting similar safety profiles. Yang *et al.* (2019a) showed the similarity, again in terms of efficacy and safety, between IBI305 and Bevacizumab. Schwabe *et al.* (2022) demonstrated the pharmacokinetic equivalence between the biosimilar of Tocilizumab (MSB11456),

the original drug authorized in the United States and approved in the European Union (EU), and other reference drugs. Cornes and Krendyukov (2019) showed general cost savings of the biosimilar drug Filgrastim in oncology, while Yang *et al*. (2019b) highlighted highly comparable efficacy and safety profiles between antitumour biosimilars and reference biological drugs in oncology. Wan *et al*. (2021) established the therapeutic equivalence between MIL60 and Bevacizumab when combined with paclitaxel/carboplatin. Finally, the randomized controlled trial by Shi *et al*. (2021) compared the efficacy and safety of LY01008 with Avastin in the first-line treatment of Chinese patients with advanced or recurrent non-squamous non-small cell lung cancer (nsNSCLC) and demonstrated the similarity of the two drugs in terms of efficacy and safety. Verschraegen *et al*. (2022) focused on CT-P16, a biosimilar to EU-bevacizumab, demonstrating its equivalence in treating metastatic or recurrent nsNSCLC. Similarly, Cheng *et al*. (2024) examined SCT510, another bevacizumab biosimilar, and found it comparable in efficacy, safety, and pharmacokinetics to the original drug, Avastin, reinforcing the viability of biosimilars in NSCLC treatment. On the other hand, Ghanei *et al*. (2024) found that P043, an omalizumab biosimilar, effectively reduced exacerbations in moderate to severe allergic asthma without notable differences in efficacy or safety compared to the reference drug, highlighting biosimilars' potential in respiratory care.

4.1.3 Non-randomized studies. The non-randomized study by Chen *et al*. (2023), aimed at investigating the combined ability of patient characteristics to predict the response to Mepolizumab treatment in cases of severe asthma, found a marked variability in the ability of patient characteristics to predict the treatment response.

4.1.4 Observational studies. Zhao *et al*. (2023) found that a Bevacizumab biosimilar matched the original drug in treating locally advanced NSCLC, with an acceptable toxicity profile and no new adverse events (AEs). Zhang *et al*. (2024) confirmed similar findings for metastatic NSCLC. Ou *et al*. (2024) reported no clinical differences between the reference and biosimilar treatments in real-world NSCLC cases. Niazi (2023) analysed synthetic RNA product costs, predicting strong market potential. Ananyeva *et al*. (2021) demonstrated the efficacy and tolerability of the rituximab biosimilar Acellbia (ACB) in patients with interstitial lung disease associated with systemic sclerosis (ILD-SSc).

4.1.5 Model-based studies. Luo *et al*. (2022) evaluated the cost-effectiveness of first-line LY01008 combined with platinum-based ChT versus ChT alone for advanced or recurrent non-squamous NSCLC in China. Using a Markov model, they analysed survival probabilities, AEs, and healthcare costs. LY01008 combined with ChT increased effectiveness by 0.48 QALYs but raised costs by 189,988 CNY (26,240 USD), resulting in an ICER of 375,425 CNY (54,430 USD)/QALY. Another analysis showed an ICER of 221,579 CNY (32,125 USD)/QALY. Findings suggest LY01008 is likely cost-effective compared to ChT alone. Goulart and Ramsey (2011) developed a Markov model demonstrating that, compared to ChT alone, the combination of bevacizumab and ChT increased average QALYs by 0.13, with a lifetime incremental cost of $72,000 per patient. This resulted in an incremental cost-utility ratio (ICUR) of $560,000 per QALY. Considering a threshold of $100,000 per QALY, bevacizumab did not appear to be cost-effective when added to ChT in patients with advanced NSCLC. Yang *et al*. (2021) assessed the financial impact of introducing bevacizumab-bvzr, a biosimilar of Bevacizumab, in the U.S. healthcare system using a budget impact model (BIM) over five years. Assuming gradual market uptake, annual savings of 313,363 USD for 10 million health plan subscribers and 92,880 USD in year one were estimated. Over five years, cumulative savings reached 7,030,924 USD (0.012 USD per member per month–[PMPM]) for commercial payers and 4,059,257 USD (0.007 USD PMPM) for the healthcare system. Over half of the savings benefited mCRC patients, highlighting significant cost benefits of bevacizumab-bvzr's adoption. Wang *et al*. (2021) assessed the cost-effectiveness of Atezolizumab + ChT versus ChT alone as a first-line treatment for extensive-stage SCLC in the USA. They used parametric survival and cure models, drawing cost data from Medicare and Medicaid. Atezolizumab + ChT increased QALYs by 0.10–0.11, but at a high incremental cost of 84,257 USD. The ICUR ranged from 785,848 to 827,610 USD/QALY. Their findings

suggest that Atezolizumab + ChT is not a cost-effective option for first-line treatment of extensive-stage SCLC. Gourzoulidis *et al.* (2020) assessed the cost-effectiveness of Lorlatinib, a third-generation anaplastic lymphoma kinase inhibitor, for treating advanced NSCLC in Greece using a three-state health survival model. Compared to platinum-based ChT, Lorlatinib was more effective, yielding 2.4 additional life years (LY) and 1.5 QALY. Though its total cost was higher (81,754 EUR vs. 12,343 EUR for ChT), its ICERs were 28,613 EUR per LY and 46,102 EUR per QALY. Probabilistic sensitivity analysis confirmed the findings, supporting Lorlatinib as a cost-effective option.

4.2 Modelling CEA and efficacy analysis

4.2.1 CEA. The CEA models used in the articles selected for the systematic review are the Markov models and Decision tree models.

4.2.1.1 Markov models. Luo *et al.* (2022) compared LY01008 plus carboplatin/paclitaxel to ChT alone, demonstrating an indirect CEA within the Chinese healthcare system. Wang *et al.* (2021) evaluated Atezolizumab plus ChT by defining three health states to estimate costs and outcomes. Gourzoulidi *et al.* (2020) analysed Lorlatinib versus platinum-based ChT using survival modelling. Meanwhile, Goulart and Ramsey (2011) found that adding Bevacizumab to ChT was not cost-effective for advanced NSCLC.

4.2.1.2 Decision tree models. Malapelle and Rossi (2019) conducted a sensitivity analysis with patients randomized into three arms to perform a CEA of Bevacizumab plus ChT versus ChT alone.

4.2.2 Efficacy analysis. In the included papers, the efficacy analysis has been conducted through Correlation models, Survival analysis, ORR, Covariance analysis models (ANCOVA).

4.2.2.1 Correlation models. Moir (2023) examined real-world evidence on biosimilars in breast and lung cancer treatments, comparing trastuzumab biosimilars with the reference drug in neoadjuvant ChT. Yang *et al.* (2021) developed a BIM to assess the financial implications of introducing bevacizumab-bvzr into U.S. healthcare, comparing biosimilars versus the reference product. Chen *et al.* (2023) identified high variability in predicting mepolizumab response for severe eosinophilic asthma, finding that covariates were more effective predictors of asthma control than exacerbation frequency.

4.2.2.2 Survival analysis. Yang *et al.* (2019a) confirmed the similarity between IBI305 and Bevacizumab in treating NSCLC using Kaplan–Meier and Cox model analyses. Wan *et al.* (2021) found MIL60 therapeutically equivalent to Bevacizumab when combined with paclitaxel/carboplatin for NSCLC. Cornes and Krendyukov (2019) highlighted cost savings of Filgrastim biosimilars in ChT. Yang *et al.* (2022b) conducted a meta-analysis showing no significant differences between Bevacizumab biosimilars and Avastin in NSCLC treatment. Ananyeva *et al.* (2021) validated the efficacy and safety of ACB, a Rituximab biosimilar, in treating interstitial lung disease associated with systemic sclerosis (ILD-SSc).

4.2.2.3 Overall response rates. Syrigos *et al.* (2021) conducted a large-scale, multicenter, double-blind trial confirming the efficacy and safety of FKB238 compared to Bevacizumab. Their findings were supported by Shi *et al.* (2021), who assessed overall response rate (ORR) as the primary endpoint, with secondary measures including disease control rate, duration of response, progression-free survival (PFS), overall survival (OS), and safety. A comprehensive meta-analysis by Xiao *et al.* (2022) reinforced these conclusions, evaluating ORR, PFS, OS, and AEs, with similar results echoed by Xu *et al.* (2022) and Zhao *et al.* (2023). Xu *et al.* (2022) employed hazard ratio and confidence intervals (CIs) to assess PFS and OS, while Zhao *et al.* (2023) quantified ORR risk ratios and differences, finding no significant deviations between the biosimilar and its reference drug. Beyond NSCLC, Kotoulas *et al.* (2022) found that omalizumab significantly improved asthma control, reducing exacerbations. Yang *et al.* (2019b) conducted a meta-analysis confirming the efficacy and safety of biosimilars in oncology, analysing ORR, anti-drug antibodies, neutropenia, and adverse drug events, though

without PFS or OS data. Zhang *et al*. (2024) carried out a retrospective study showing an ORR comparable to Bevacizumab, with only slight differences in AEs. Verschraegen *et al*. (2022) verified the equivalence of CT-P16 and EU-Bevacizumab in a randomized phase III trial, finding nearly identical ORRs within set equivalence margins. Russo *et al*. (2017) further reinforced Bevacizumab's positive impact when added to first-line ChT for advanced NSCLC. Comparative analyses also highlighted the similarity of biosimilar treatments. Ou *et al*. (2024) showed no significant differences between Bevacizumab biosimilars (CT-BB) and the reference product (CT-RP) in ORR or disease control rates. Cheng *et al*. (2024) evaluated SCT510 against Bevacizumab, revealing similar ORRs at weeks 12 and 18, indicating comparable clinical efficacy, safety, immunogenicity, and pharmacokinetics.

4.2.2.4 ANCOVA models. Schwabe *et al*. (2022) demonstrated the pharmacokinetic equivalence between MSB11456 and Tocilizumab, both authorized in the United States and approved in the EU, with the reference drugs. The primary pharmacokinetic parameters, transformed into logarithms, were analysed using an analysis of covariance (ANCOVA) model. From this model, the 90% CI for the difference in mean parameters between the three groups (MSB11456 compared to US-authorized tocilizumab, MSB11456 compared to EU-approved tocilizumab, and US-authorized tocilizumab compared to EU-approved tocilizumab) was calculated, and then re-expressed on the original ratio scale to evaluate equivalence. Ghanei *et al*. (2024) used the ANCOVA model to analyse variations in spirometric measurements (FEV1). All patients who received at least one dose of the study drug were included in the safety population.

5. Discussion

In the field of health economics, numerous studies have delved into the intricate relationship between the use of pharmaceutical products and the variations in life quality (Magazzino *et al*., 2024). Our research offers a comprehensive analysis of existing literature on cost effectiveness and efficacy analysis of biosimilar drugs for lung diseases, addressing health-related issues from various viewpoints. Of the 2,852 papers retrieved, only 28 articles published in peer-review journals have met our inclusion criteria. Our findings can foster the usage and development of quantitative models in the health field and assist scholars and practitioners in establishing best practices.

After a careful analysis of the results, we can answer the four research questions addressed.

With respect to RQ1, biosimilar drugs have been found to be more economically advantageous compared to traditional and biological drugs according to the studies we coded with the numbers 8, 10, and 34. Improvements in asthma control (no. 22) and increases in QALY were also reported, although accompanied by higher costs (numbers 1, 26, 35, and 44) or a higher cost-utility ratio (no. 23). All other studies showed a substantial equivalence in terms of efficacy and safety between biosimilar and traditional drugs.

Regarding RQ2, we have not found any particular circumstances that generated different levels of economic convenience, except for the consideration that in cases where the biosimilar was added to ChT alone, the greater efficacy of the treatment logically generated higher costs (numbers 1, 23, 26, and 44).

In relation to RQ3, the main lung diseases in which biosimilar drugs have been used are lung cancer (no. 34), small cell lung carcinoma (no. 26), non-small cell lung carcinoma (no. 23, 37, 38, 41, 42, 44, 46), severe allergic asthma (numbers 16, 22, and 45), unresectable, metastatic, or recurrent non-squamous non-small cell lung carcinoma (no. 20), non-squamous non-small cell lung carcinoma (numbers 3, 15, 22), recurrent non-squamous non-small cell lung carcinoma (18 and 40), locally advanced and advanced non-small cell lung carcinoma (5), advanced non-small cell lung carcinoma (4), and interstitial lung disease associated with systemic sclerosis (47).

Finally, considering RQ4, we distinguish between the two analyses. For CEA, papers 1, 26, 35, and 44 in conducting the CEA used Markov models. These models allow for economic evaluations in healthcare as they take into account both costs and clinical outcomes,

considering various alternatives for the treatment of chronic diseases and providing support for problems involving decisions under uncertainty over a continuous period. Markov models are ideal for representing repetitive events, can be adapted to various types of data, and require fewer parameters than other models, making them versatile for different applications, with faster processing times and reduced costs. However, Markov models consider patients in a discrete and not continuous health state, with events representing the transition from one state to another. This can be a problem in evaluating continuous evolutionary dynamics as a consequence of different scenarios. In these cases, decision trees, as in Malapelle and Rossi (2019), are more effective.

Among the models used for efficacy analysis, Moir (2023) and Yang *et al*. (2021) applied the correlation method, not assessing causality, while Yang *et al*. (2019a), Cornes and Krendyukov (2019), Yang *et al*. (2022b) and Ananyeva *et al*. (2021) the survival analysis, which has the main advantage of including patients who do not complete the trial or do not reach the study endpoint (censored data), comparing the number of survivors in each group at different time points. Papers 2, 3, 17, 20, 22, 37, 40, 41, 42, and 46 conducted ORR analysis since this analysis method requires smaller sample sizes and shorter follow-up times. The therapeutic effect is attributed to the drug, excluding the natural course of the disease, and is usually based on objective and quantitative evaluations. However, the use of ORR alone may not adequately describe the antitumour activity of the experimental drug, hence the need for a simultaneous descriptive analysis of the duration and time to response. Schwabe *et al*. (2022) and Ghanei *et al*. (2024) used the ANCOVA model since it allows the isolation of the effects of the independent variable on the dependent variable. However, it is not suitable for small size samples.

Our findings highlight the increasing confidence in biosimilars as viable, cost-effective substitutes for their reference biologics. The evidence strongly supports their ability to deliver equivalent therapeutic outcomes, which could enhance patient access to critical treatments while upholding rigorous safety and efficacy standards. Notably, the availability of biosimilars in oncology is increasingly recognized as a key strategy for ensuring the financial sustainability of healthcare systems (see, Huang *et al*., 2020). Furthermore, all the studies examined mainly focus both on the OECD region, where biosimilar regulations adhere to similarly stringent criteria (e.g. Esteban *et al*., 2019; Liu *et al*., 2019; Huang *et al*., 2020; Rathore and Bhargava, 2020), and on China, Taiwan, and Iran, which implements international standards closely aligned with those of other nations (Chan *et al*., 2018; Kang *et al*., 2021; Rahalkar *et al*., 2021; Safardoust *et al*., 2025) [3].

Nevertheless, at the end of the analysis, it is important to acknowledge certain limitations of our systematic review. Firstly, the process of selecting literature may have been constrained by the omission of some pertinent articles not included in the Dimensions database, neither Web of Science nor Scopus, as well as of book chapters and conference papers not included among peer-reviewed journals. Secondly, while the time frame analysed is quite wide, choice of keywords might have led to the exclusion of other relevant studies. Thirdly, publication bias should be recognized since studies with ineffective or inconclusive findings may be underrepresented in published literature, leading to a distorted perception of their effectiveness. Finally, despite adhering to the systematic review methodology to ensure replicability, a certain level of subjectivity is inevitable. In this context, future research directions could explore the application of machine learning techniques, like topic modelling, since these methods are devoid of human bias.

6. Conclusions

As healthcare systems worldwide face financial constraints, the need for cost-effective treatment options continues to rise. One of the key solutions to this challenge are biosimilars medications. Over the last twenty years, the research area inherently the investigation about cost effectiveness and efficacy of biosimilar drugs in the medical area of lung diseases has experienced substantial growth and, as far as we are aware, it has not been systematically

reviewed yet. To fill this gap, this paper enhances the understanding of biosimilars in lung diseases and their cost-effectiveness and efficacy, resulting valuable for both scholars and policymakers pointing to explore the integration of these new drugs into the healthcare and pharmaceutical system. Since the selected studies are quite recent, it underlines the cutting-edge nature of this research area in the health economics field.

In conclusion, our findings mainly report that biosimilar drugs are more cost-effective than traditional and biological drugs, with improvements in asthma control and QALY, though at higher costs in certain cases, and have similar efficacy. No specific condition alters their economic benefits, except when combined with ChT. In addition, they are used in various lung diseases, including different types of lung carcinoma and severe allergic asthma. Although most results showed equivalence in terms of efficacy and safety between biosimilar drugs and their corresponding traditional drugs, some research found that adding the biosimilar to ChT treatment led to an increase in life expectancy or QALYs. On the other hand, the addition of the biosimilar also generated an increase in costs. Consequently, the ICERs were positive with a wide range between minimum and maximum values. In fact, depending on the cases, they reported values ranging from $28 USD/QALY to $965 USD/QALY. Finally, this systematic review has highlighted that in the area of lung diseases, both for CEA and efficacy analysis, most studies followed a traditional approach consisting of modelling techniques such as Markov models and Decision tree for CEA, Correlation, ORR, Survival and Covariance analysis for the efficacy. However, the methodology applied should be better explained since the articles mainly focus on the results. Moreover, their modelling approach not properly considered the five areas recommended by Caro and Möller (2014), namely conceptualization, model structure, uncertainty, model validation, and transparency.

By adding to the current body of research, our results provide meaningful insights for the policymakers. Spending in public health care services is often regarded as a tool for promoting both fairness and efficiency within an economy, largely because of its ability to redistribute resources effectively (Gamlath and Lahiri, 2019), and especially considering the positive relationship between health spending and aggregate economic effects in the long run (Pereira *et al*., 2019). In this sense, biosimilar drugs, if used appropriately, constitute a way to make resources available to be allocated to more effective innovative tools.

Moreover, even if this field of research is large and still in its early stages, the results found in the analysed literature are already useful to help practitioners in identifying best practices, modelling technique, and to guide future health policies in the pharmaceutical field.

As governments, healthcare providers, and patients seek sustainable ways to manage medical expenses without compromising quality, biosimilars are emerging as a promising component in the evolution of health and pharmaceutical economics. From a policy perspective, the usage of the most appropriate modelling strategy may help in obtaining a clearer insight of the current landscape and enables policy makers to allocate additional funding for the adoption of cost-effective biosimilars in specific healthcare areas, improving patient outcomes and potentially reducing public health expenditure. However, the choice to use the original or biosimilar drug must be made by the physicians and cannot be driven only by economic criteria.

Considering that the studies investigated concentrate mainly on developed nations, as a promising avenue for further research, scholars could focus their attention on biosimilar adoptions and regulations in lagging countries. Further investigations may explore how different modelling approaches may lead to different results for biosimilars' use in specific lung diseases, particularly in areas where evidence is currently lacking, or conduct long-term follow-up studies to assess the sustained economic impact and clinical outcomes of defined biosimilar treatments.

Authors' contributions

All authors contributed to the study design, literature search, as well as writing, and review and approval of the manuscript.

Data availability statement
The data will be made available upon request.

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Notes

1. As robustness check, the search was conducted on the Web of Science and Scopus databases. Given the smaller number of records identified and since the selected documents overlapped with those already retrieved, these records were not taken into consideration.
2. The number of papers included is in line with previous systematic literature review on biosimilars' economic evaluation (e.g. 21 in D'Angiolella *et al*., 2018; 17 in Huang *et al*., 2020; 12 in Liu *et al*., 2019; 27 in Li *et al*., 2021).
3. Biosimilar regulations slightly vary across these regions, reflecting different priorities. The EU's EMA mandates comparisons with EU-authorized reference drugs, ensuring consistency, while China permits both local and international references for flexibility. Clinical trial requirements differ, with China sometimes requiring data specific to local populations. The U.S. FDA enforces stricter rules, requiring identical dosage forms and strengths, applying case-by-case evaluations, and imposing stringent interchangeability standards, complicating substitution. Japan's PMDA does not regulate interchangeability, requiring prescriber approval and comparative studies for biosimilar use, primarily in hospitals. New Zealand's Medsafe aligns with EMA guidelines but incorporates cost-effectiveness through Pharmac. The UK's MHRA mostly follows EMA principles, while Great Britain uses a comparability program instead of efficacy studies. Taiwan's TFDA mandates biosimilars match a locally approved reference product with extensive comparative studies. Iran's IFDA adheres to international standards but emphasizes local production to reduce imports, though interchangeability policies remain ambiguous.

Supplementary material
The supplementary material for this article can be found online.

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