Evaluation of Clinical Value of Siltuximab in Castleman Disease Based on Multi-criteria Decision-making

Li Jiaxun[1], Guo Xiaoming[2], Zhang Fang[3*], Dong Li[1*]

(1. School of Business Administration, Shenyang Pharmaceutical University, Shenyang 110016, China;
2. Department of Pharmacy, Liaoyang Liaohua Hospital, Liaoyang 111000, China;
3. ZTE Foundation HTA Center, Shenzhen 518087, China)

Abstract

Objective To evaluate the clinical value of siltuximab in the treatment of Castleman disease based on multi-criteria decision analysis (MCDA) and evidence and value: Impact on decision making (EVIDEM) framework. **Methods** The evidence matrix for quantitative analysis of MCDA was extracted through literature research, and the weight of each evaluation index was calculated by the maximum differentiation measure in conjoint analysis. Besides, the clinical value of siltuximab in the treatment of Castleman disease was analyzed quantitatively and qualitatively based on the results of expert questionnaire surveys. **Results and Conclusion** The clinical value score of siltuximab was 0.491, and the weight ratio of "therapeutic benefit" (15.39%), "drug effectiveness" (14.46%) and "drug safety" (11.43%) were the three largest. Among the indexes of "drug effectiveness" "drug safety" "patient reported outcome" "therapeutic benefit" and "non-medical cost", siltuximab for Castleman disease was considered to be a more valuable treatment option than other first-line therapies. By qualitative analysis, 57% experts believed that siltuximab was a better treatment option. The indexes that contribute the most to the overall clinical value of siltuximab are " therapeutic benefit" "drug effectiveness" and "quality of evidence", while the indexes that have a negative impact on the clinical value of siltuximab is "drug treatment cost".

Keywords: multi-criteria decision analysis; orphan medicinal product; Castleman disease; conjoint analysis; clinical value

Treatments developed for rare diseases are known as orphan medicinal products (OMPs). OMPs may bring benefits to areas where the treatment demand is seriously unsatisfied. Because of the lack of evidence of clinical benefit, high cost of treatments, and short-term clinical outcomes, OMPs often exceed cost effectiveness thresholds in health technology assessment (HTA). Besides, its access may be based on the results of a small trial or uncontrolled trial, making the access to OMPs more challenging [1]. Multiple criteria decision analysis (MCDA) is a decision-making tool that considers multidimensional factors to compare healthcare technologies by combining

* Corresponding author: Zhang Fang, associate professor. Major research area: Health economic policy evaluation, pharmacoeconomic methodology research. Tel: 18341400097, E-maill: zhang.fang5@zte.com.cn; Dong Li, associate professor. Major research area: Pharmaceutical administration, pharmaceutical intellectual property research. Tel: 024-23986543, E-mail: sydongli@163.com.

individual criteria into a holistic assessment [2, 3]. MCDA experts believe that the MCDA criteria are clear and can measure the comprehensive value of drugs from multiple perspectives to solve the challenges of rare disease drug evaluation. Both theory and practice show that MCDA is applicable to the comprehensive clinical evaluation of rare diseases, and it is recommended o apply the evidence and value: Impact on decision making (EVIDEM) framework for the comprehensive clinical evaluation of rare disease drugs [4].

Castleman disease (CD) is one of the first rare diseases included in the catalogue of China, which can be divided into unicentric (UCD) and multicentric (MCD) according to the area of lymph node involvement [5]. Patients usually have multiple giant lymph node, fever, malaise, liver and kidney insufficiency and other systemic manifestations, which severely affect their daily life and have high disease mortality. Therefore, they need timely diagnosis and treatment.

The "Expert Consensus on the Diagnosis and Treatment of Castleman Disease in China (2021 Edition)" [5] recommends "siltuximab ± prednisone, TCP regimen (thalidomide + cyclophosphamide + prednisone), R-CVP regimen (rituximab + cyclophosphamide + vincristine + prednisone), and rituximab ± prednisone" as the first-line treatment options for MCD. The only randomized double-blind controlled study in the treatment of idiopathic MCD (iMCD) confirmed that 34% of patients achieved sustained tumor and symptom remission and demonstrated that cytokines, including interleukin-6 (IL-6), played a key role in the pathogenesis of iMCD [6]. Based on a prospective phase II clinical study, 48% of patients with a TCP regimen achieved sustained tumor and symptom remission with grade 3 or higher rash (4%) and pneumonia (4%) [7]. Although there is no prospective evidence-based evidence for rituximab, some experts also recommend it as a first-line treatment option for non-severe iMCD based on data from case reports and retrospective studies. In this paper, "TCP regimen, R-CVP regimen, and rituximab ± prednisone" are referred to as "other first-line treatment options".

Siltuximab is an anti-IL-6 human-mouse chimeric monoclonal antibody that blocks the binding of human IL-6 to the IL-6 receptor, producing an inhibitory effect on IL-6. On December 2, 2021, siltuximab was approved for marketing in China, providing more treatment strategies for diseases and more options for patients. Based on the EVIDEM framework, this paper analyzes the clinical value of siltuximab for the treatment of MCD, using MCD and siltuximab as the study subjects and the health care system as the research perspective.

1 EVIDEM framework

The EVIDEM framework was provided by the EVIDEM Collaboration, a nonprofit organization that developed the framework with research institutes based on criteria from an extensive literature analysis and a detailed analysis of drug decision processes in more than 20 regions worldwide. The MCDA model was constructed by selecting a set of criteria that meet the MCDA modeling principles, including completeness, non-redundancy, operationalization, and mutual independence [8].

The decision indicators included in the EVIDEM framework are used to collect, analyze, evaluate, synthesize, and present evidence for each decision to form the MCDA evidence matrix, the framework is shown in Table 1. The EVIDEM framework can be divided into two research phases, the core modeling guidelines for quantitative analysis and the scenario-based guidelines for qualitative analysis [8]. The quantitative indicators in this study refer to "Expert Consensus on Application of Multi-Criteria Decision Analysis to Comprehensive Clinical Evaluation of Rare Disease Drugs" [4].

Table 1 Quantitative indicators of EVIDEM framework

Primary indicator	Secondary indicator
The necessity for drug intervention	D1: Disease severity
	D2: Size of affected population
	D3: Unmet needs
Results of drug intervention	I1: Comparative effectiveness
	I2: Comparative safety
	I3: Patient-reported outcomes
Benefits of drug intervention	T1: Type of preventive benefit
	T2: Type of therapeutic benefit
Economics of drug intervention	E1: Cost of intervention
	E2: Other medical costs
	E3: Non-medical costs
	E4: Health care fund affordability
Evidence of drug use	Q1: Quality of evidence
	Q2: Consensus/clinical practice guidelines
Other	O1: Innovation of intervention

2 Research methods and contents

2.1 Literature research

In this study, we searched Chinese databases such as CNKI, Wanfang and VIP and foreign databases such as PubMed and Embase. Then, the targeted literature search strategies were developed based on different evaluation dimensions and different evaluation indexes involved in the evaluation framework to form different literature databases. Finally, literature search and data extraction were conducted based on the EVIDEM framework to form an evidence matrix.

2.2 Maximum difference scaling

The maximum difference scaling (Maxdiff) in conjoint analysis is one of the methods used to analyze participant preferences, which was formally introduced into healthcare research by McIntosh and Louviere [9]. Maxdiff can be used to calculate each respondent's score for each indicator through a Hierarchical Bayesian (HB) algorithm. The differences between the most and the least important indicator coefficients are taken as a measure of indicator importance. The relative importance of each indicator is calculated by normalizing the indicator weight measure to 1, which means that the relative importance of the indicator is the proportion of the joint contribution to the importance of all indicators. Studies have indicated that Maxdiff is less cognitively taxing on participants, making it easier for Maxdiff to achieve its purpose of investigating healthcare topic preferences [10].

The maximum variance measure was conducted by Sawtooth software, and stakeholders were invited to participate in the first stage of the questionnaire to obtain the weights of each indicator.

2.3 Quantitative and qualitative analyses

Quantitative and qualitative analyses were performed by Microsoft Excel to complete the second and third phases of the survey, respectively [11]. The quantitative analysis was used to calculate the weight and value contribution. In the qualitative analysis, experts scored the qualitative indicators based on the

results of the quantitative analysis to qualitatively analyze the value of the drug in a particular aspect. Quantitative indicators were evaluated using a direct rating scale with scores ranging from 0 to +5 for non-comparative indicators and −5 to +5 for comparative indicators, and the value contribution (VC_x) of each quantitative indicator was calculated as the product of its normalized weight (W_x, $\sum W_x = 1$) and the standardized score (S_x = Non-comparative standard score/5; S_x = Comparative standard score/10). The total value estimated (VT) was the value of all indicators:

$$VT = \sum_{x=1}^{n} VC_x = \sum_{x=1}^{n} (W_x \times S_x).$$

Contextual indicators were evaluated using a qualitative scale that converted the positive, neutral, or negative effects of the study results into numerical scales, i.e., +1, 0, and −1 scores, respectively.

3 Document retrieval

3.1 Literature retrieval strategy

The literature search databases included CNKI, Wanfang, VIP, PubMed, Embase, and Cochrane, in order to comprehensively and systematically search the literature related to the disease burden and treatment status of CD. The main Chinese search terms were “Castleman disease” “life quality” “burden of disease” “status of patient” “guideline” “safety” “effectiveness” and so on. The main English search terms were “Castleman’s disease” “incidence” “prevalence” “quality of life” “global burden of disease” “disease management” “guideline” “clinical trial”, etc. The search period was from the date of database creation to September 1, 2022.

3.2 Inclusion and exclusion criteria

The retrieved literature included phase 2−4 randomized controlled trials and prospective studies due to the small number of rare disease studies, the small number of patients, and the limited number of patients involved in clinical trials. Meanwhile, it excluded literature with only study abstracts, non-English and non-Chinese literature, literature with no access to full text, and trials or case reports without research data. The literature screening process is shown in Fig. 1.

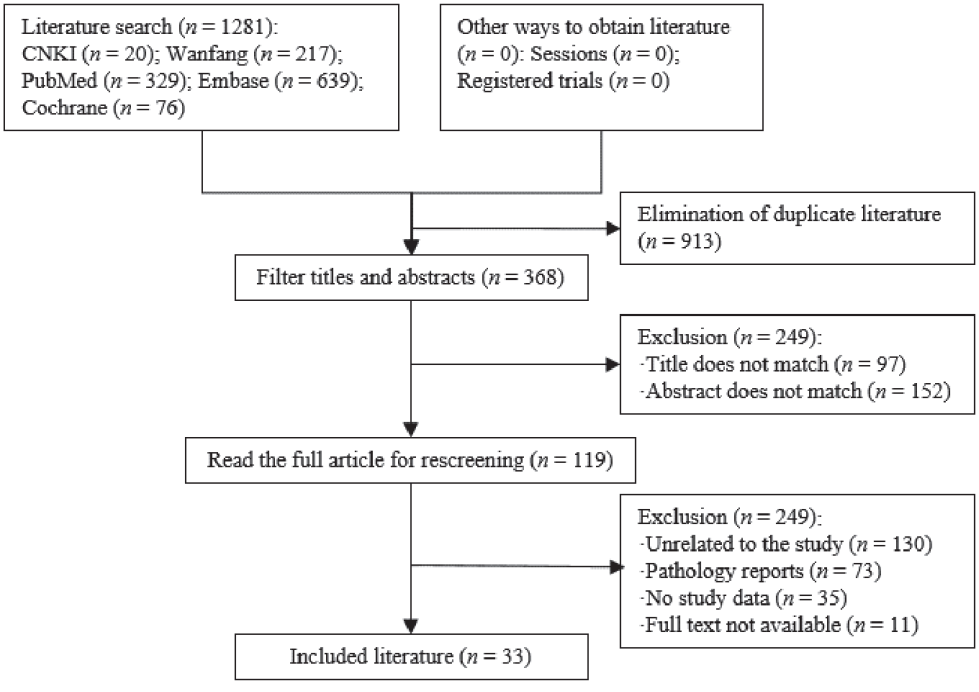

Fig. 1 Literature screening flow chart

3.3 Literature search results

The literature screening was completed according to the inclusion and exclusion criteria and the literature screening process. 7 epidemiological papers on Castleman disease, 2 papers on patient quality of life, 1 paper on patient economic burden, 8 papers on patient unmet need, 6 papers on disease guidelines, and 9 papers on clinical trials were finally included.

3.4 Overview of evidence matrix

In terms of the need for pharmacological intervention, MCD disease is severe because patients often have systemic manifestations such as fever, night sweats, malaise, liver and kidney insufficiency, generalized edema, and enlarged lymph nodes [5]. Besides, patient treatment prognosis is poor, with 5-year survival rates of only 51%−77% in the literature [12]. The number of patients is small, with the incidence of CD less than 1/1 000 000 in China, except for 1/626 000 in northern China [13]. Besides, there remains a significant unmet need for CD due to disease specificity and challenges in diagnosis and treatment [14].

In terms of drug intervention outcomes, an international multicenter RCT (enrolling 79 patients, including 25 Chinese patients) demonstrated the efficacy and long-term safety of siltuximab *vs*. placebo for the treatment of iMCD, with 34% of MCD patients achieving sustained tumor and symptom remission with siltuximab therapy, a median duration of remission of 383 d, discontinuation due to adverse events of (12 cases [23%] *vs*. 10 cases [38%] 23% *vs*. 38%), and the incidence of serious adverse events was (25 cases [47%] *vs*. 14 cases [54%]) [15, 16]. In addition, subjects were reported to have early improvement in symptoms, and the results of the EQ-5D questionnaire showed that patients had a health utility value of 0.71 and a 6-month benefit of 0.096 QALYs from treatment [17].

In terms of benefit from pharmacological interventions, PFS was significantly improved in patients treated with siltuximab, with an overall survival rate of 95% (93% CI 85%−100%) at two years of PFS [18]. Real-world studies in Korea, Poland, and Italy have shown that siltuximab has a good safety profile, and the long-term treatment is well tolerated [19-21].

In terms of the economics of drug interventions, the annual costs for the drug dosage of the first-line treatment regimen were calculated based on the latest publicly available drug prices, and the content of the budget impact analysis was provided for reference.

In terms of evidence related to drug use, the Phase II RCT trial was a global multicenter randomized, double-blind, placebo-controlled trial that evaluated the product as the first and only approved treatment for rare disease MCD in China, which was the only approved drug by FDA and EMA. The only iMCD randomized controlled trial confirmed that siltuximab significantly improved 18-week sustained tumor and symptom remission rates. Besides, it also improved quality of life with a 6-year disease control rate of 97%, and survival rate of 100%, and its efficacy was consistent with real-world study. Patient-reported outcomes showed improved quality of life, which was consistent with trial results [15, 16]. “Guidelines for the management of lymphoma (2021)” published by the Chinese Society of Clinical Oncology (CSCO) [22], “Clinical Practice Guidelines for B-cell lymphoma (2021)” published by the National Comprehensive Cancer Network (NCCN) [23], and “Castleman’s Disease Management Guidelines” published by the British Society of Haematology (BSH) [14] and other guidelines recommended siltuximab as the first choice for patients with iMCD.

In terms of drug innovation, siltuximab was the first approved IL-6-targeted monoclonal antibody that filled a therapeutic gap in iMCD and was indicated for elderly patients without dosing adjustments.

4 Research results

4.1 Index weight

The first phase of the questionnaire survey was conducted in November 2022 through a web-based questionnaire, and 20 representatives, including MCD

patients, clinicians, pharmacists, health economics and health policy experts, business representatives, and public representatives, were invited to participate in the questionnaire survey for indicator empowerment, the participation of questionnaire is shown in Table 2.

Table 2 Participation in index weight calculation

Participant identity	Number of participants
MCD patient representative	4
Occupational therapists	5
Pharmacist	2
Expert in health economics and health policy	4
Company representative	2
Public representative	2
Total	20

The questionnaire used the maximization of variance measure in conjoint analysis to calculate the weights. In the questionnaire, 4 indicators were randomly selected from 15 indicators to form 1 question, and the participants were asked to select the indicators they considered the most and least important for evaluating the drug indicators among the 4 randomly generated indicators. The indicator weights were calculated by counting the total number of occurrences, the most important number of occurrences, and the least important number of occurrences for each indicator through the participants' answers to 12 questions.

The results of the data analysis showed that "therapeutic benefit from the drug" (20.87%), "drug effectiveness" (19.64%), and "drug safety" (8.01%) had the greatest weighting and were the most influential indicators in evaluating the clinical value of the drug according to the participants. The "non-medical costs" (0.70%), "other medical costs" (2.18%), and "drug innovation" (2.55%) had the least weighting. In contrast, the participants considered that costs other than the cost of drug treatment were not influential in evaluating the clinical value of drugs to a great extent, the index weight calculation results is shown in Fig. 2.

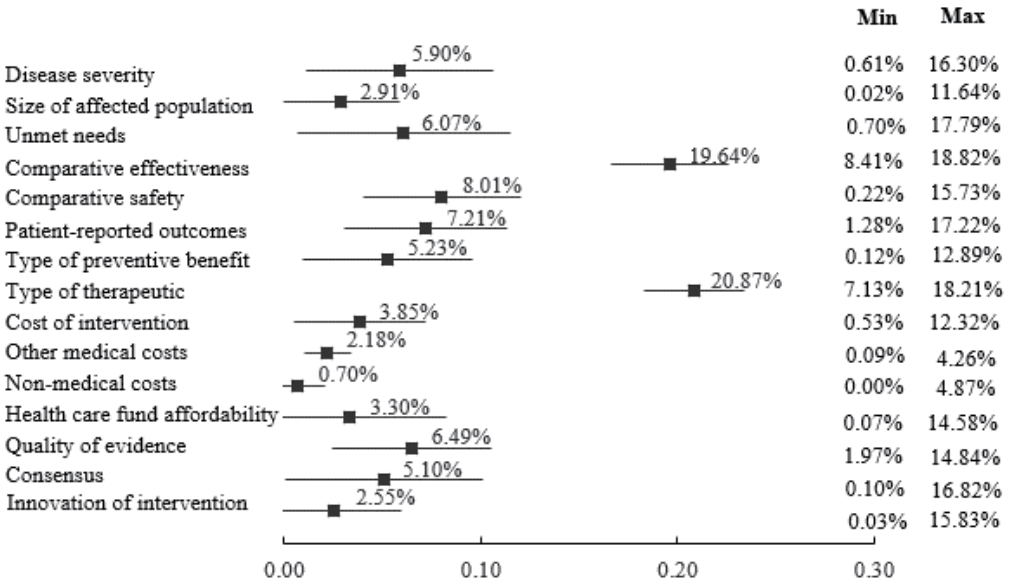

Fig. 2 Index weight calculation results

4.2 Quantitative analysis

The second phase of the questionnaire was conducted in December 2022 via a web-based questionnaire, and the four clinicians/pharmacists and three economics and health policy experts in the first phase of the questionnaire were invited to continue to participate in the second phase.

Quantitative indicators were evaluated using a direct rating scale, and each expert scored different indicators according to the content provided in the evidence matrix, with scores ranging from 0 to +5 for non-comparative indicators such as the need for drug intervention and evidence related to drug use, and from −5 to +5 for comparative indicators such as the outcome of drug intervention and the economics of drug intervention, and the mean ± standard deviation (SD) of each indicator score was calculated according to the expert scores, the quantitative score is shown in Fig. 3.

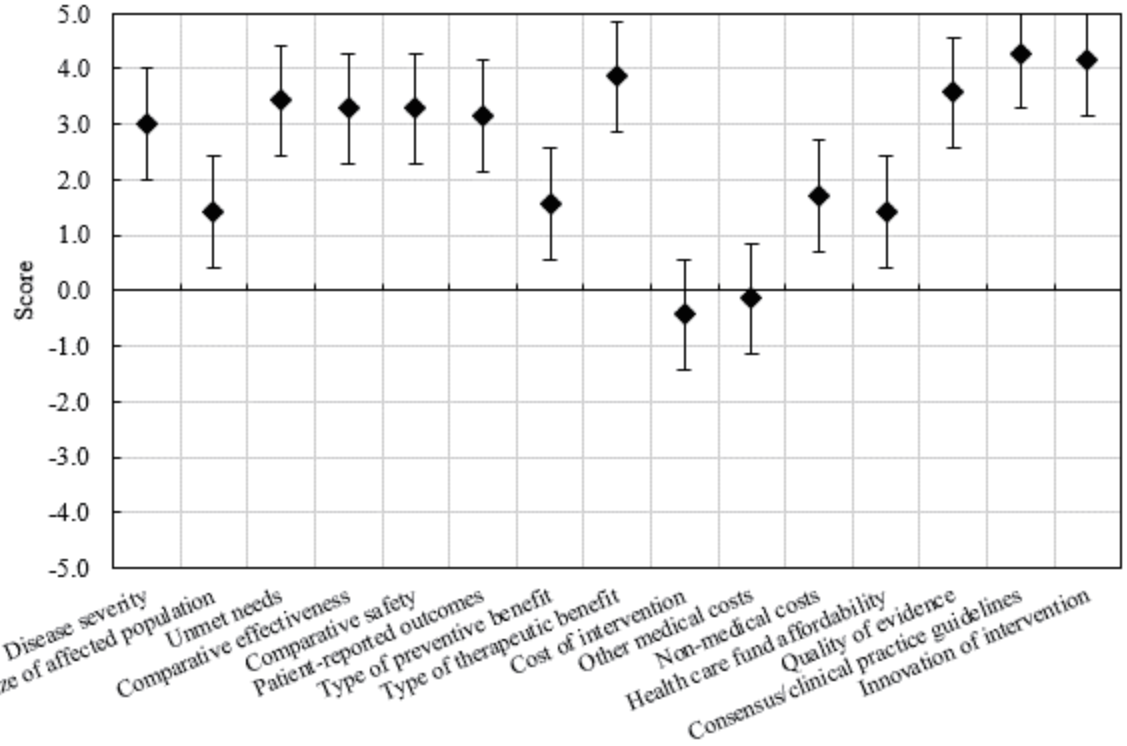

Fig. 3 Quantitative score of siltuximab

In terms of the need for pharmacological interventions (all scores were 0 to +5), the "disease severity" score was 3.00 ± 1.15, reflecting the experts' perception that the disease has an important impact on survival and patient quality of life. Since the "disease population" score was 1.43 ± 1.81, all experts considered MCD to be an extremely rare disease. As the "unmet need" score was 3.43 ± 1.27, experts considered patients with MCD to have an important unmet need for curative and effective treatments.

In terms of drug intervention outcomes (all scores were −5 to +5), the "drug effectiveness" score was 3.29 ± 0.95, and experts considered that the efficacy of siltuximab was recognized because of the reliable effectiveness data obtained in clinical trials compared with placebo. As the "drug safety" score was 3.29 ± 1.60, siltuximab was considered to have a better safety profile compared with placebo. As the "patient-reported outcomes" score was 3.14 ± 1.21, and all scores were more than 3, the safety profile of siltuximab was also considered to be better than placebo. The patient-reported outcomes also showed

improvements in health-related quality of life and benefits for patients treated with siltuximab.

With regard to the benefit of pharmacological interventions (all scores were 0 to +5), the "prevention benefit from the drug" score was 1.57 ± 1.62 and the " therapeutic benefit from the drug" score was 3.86 ± 0.83, so the experts concluded that the evidence matrix did not show a prophylactic benefit of siltuximab. However, they recognized the therapeutic benefit of siltuximab as having a positive effect in relieving symptoms, prolonging life, and reducing disease progression.

In terms of the economics of pharmacological interventions (all scores were −5 to +5), the "cost of drug therapy" score was −0.43 ± 3.26 and the "other medical costs" score was −0.14 ± 2.48. The negative scores for both scores were due to the higher publicly available prices of siltuximab. The two scores were negative because the current publicly available price of siltuximab was higher than that of conventional treatment options, which may result in additional drug treatment costs for patients and may even result in treatment costs for adverse reactions. As the "non-medical costs" score was 1.71 ± 1.80, experts believed that patients using siltuximab would reduce symptoms and decrease the frequency of follow-up visits. The "affordability of health insurance fund" score was 1.43 ± 2.23, which means that due to the high cost of innovative OMPs, there was a certain impact on the health insurance fund. But the number of patients with rare diseases was limited, so the impact on the affordability of health insurance fund was not too great.

In terms of evidence from those involved in drug use (all scores were 0 to +5), the "quality of evidence" score was 3.57 ± 0.98, which showed that experts highly recognized the validity of the evidence, the completeness of the report, and the relevance of the evidence from clinical trials. In addition, the "expert consensus/clinical guideline" score was 4.29 ± 0.49, and the "drug innovation" score was 4.14 ± 0.69. As a new drug recommended by domestic and international clinical guideline experts, the positive score of siltuximab also showed the experts' recognition of its innovation and efficacy.

4.3 Clinical value contribution

The evaluation score of each indicator was adjusted to the relative importance assigned to each indicator, which was used to calculate the overall value contribution of each indicator for clinical value contribution for MCD. The value contribution (VC_x) of each quantitative indicator was calculated as the product of its normalized weight (W_x, $\sum W_x = 1$), the standardized score (S_x = Non-comparative standard score/5; S_x = Comparative standard score/10), and the total value estimate (VT) was the sum of the value contributions of all indicators:

$$VT = \sum_{x=1}^{n} VC_x = \sum_{x=1}^{n} (W_x \times S_x).$$

Based on the formula, the clinical value score obtained by multi-criteria decision analysis for siltuximab was 0.491. Therefore, siltuximab for MCD was considered a more valuable treatment option among the following quantitative MCDA indicators (drug effectiveness, drug safety, patient-reported outcomes, therapeutic benefit from the drug, and non-medical costs). But the cost of drugs and other treatment costs were higher than typical treatment options.

A multi-criteria decision analysis yielded a value score of 0.491 for siltuximab for Castleman disease, with a positive value estimate of the added value of siltuximab compared with other first-line treatment options [11, 24]. Among the quantitative indicators "drug effectiveness" "drug safety" "patient-reported outcomes" "therapeutic benefits" and "non-medical costs", the value contribution of Siltuximab was the highest and it was considered a more valuable treatment option for Castleman disease. However, in terms of drug costs and other treatment costs, the assessment of the value of siltuximab was negatively affected by the higher cost of siltuximab compared with other first-line treatment options, the weighted contribution is shown in Fig. 4.

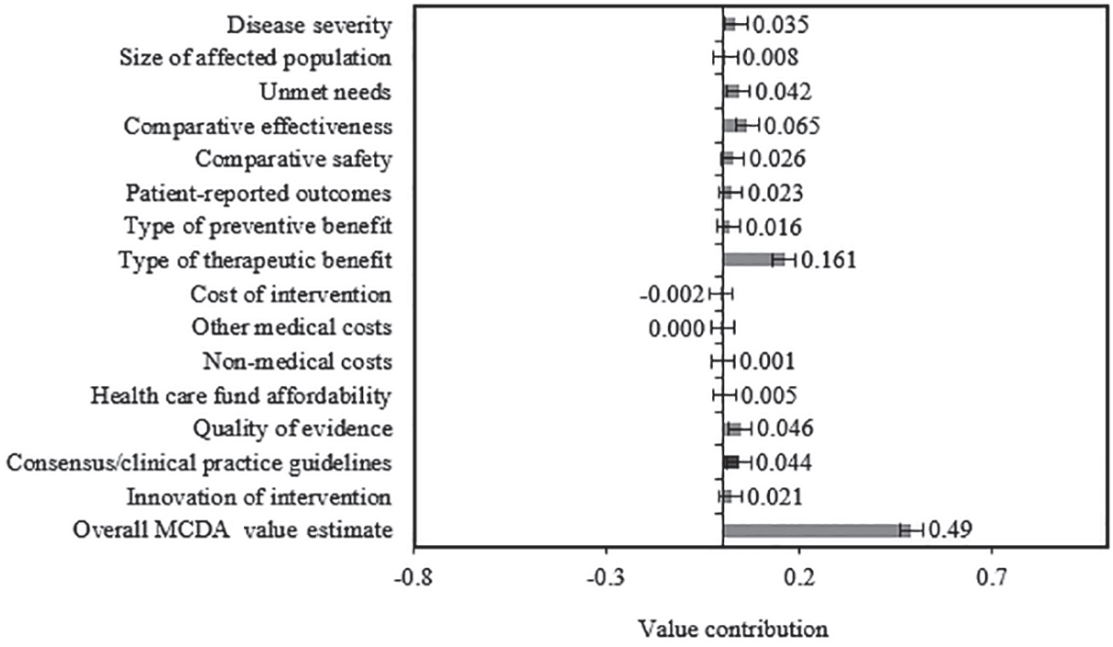

Fig. 4 Weighted contribution of siltuximab

4.4 Qualitative analysis

The third phase of the questionnaire was conducted in December 2022 via a web-based questionnaire, and the five clinicians, pharmacists, and economics and health policy experts in the first phase of the questionnaire were invited to continue participating in the third phase. Participating experts rated the positive, neutral, or negative impact of each qualitative criterion based on the results of the evaluation of siltuximab in terms of normality of use and accessibility of use, with 57% of experts considering siltuximab to be a valuable treatment option,the qualitative analysis results is shown in Fig. 5.

In terms of a positive impact of "alignment with the mission and goals of the health care system", 80% of experts believed that siltuximab would have a positive impact because its therapeutic benefits and drug effectiveness were consistent with goals of health care. However, 20% of experts only believed that siltuximab would have a neutral impact because the limited prevalence of MCD would not have much impact on this indicator. 60% of experts believed that stavudine was consistent with priority populations and health care system accessibility, and siltuximab was aligned with the current priority populations of the health system plan. As MCD is recognized as a rare disease, the severity of the disease makes treatment more likely to involve innovative therapies. In terms of "common goals and specific benefits", 60% of experts believed that siltuximab would have a positive impact and that there was a disease unmet need for MCD, but the limited prevalence kept 40% of experts neutral. In terms of "environmental impact", 60% of experts were neutral on the extent of environmental damage caused by the production and use of siltuximab, and the evaluation evidence did not clearly show its environmental impact. In terms of the "capacity of the health system and rational use of drugs", 40% of experts believe that it has a positive impact, that siltuximab is easy to use and can be used in the elderly without dose adjustments, 40% are neutral, and 20% believe that it may have a negative impact and that there may be a risk of irrational use of drugs. In terms of "political, historical and cultural context", 60% of the experts believed that siltuximab would have a positive impact and it is the first and only anti-IL-6 targeted monoclonal antibody approved for the treatment of iMCD in China, which is in line with the priority of innovation.

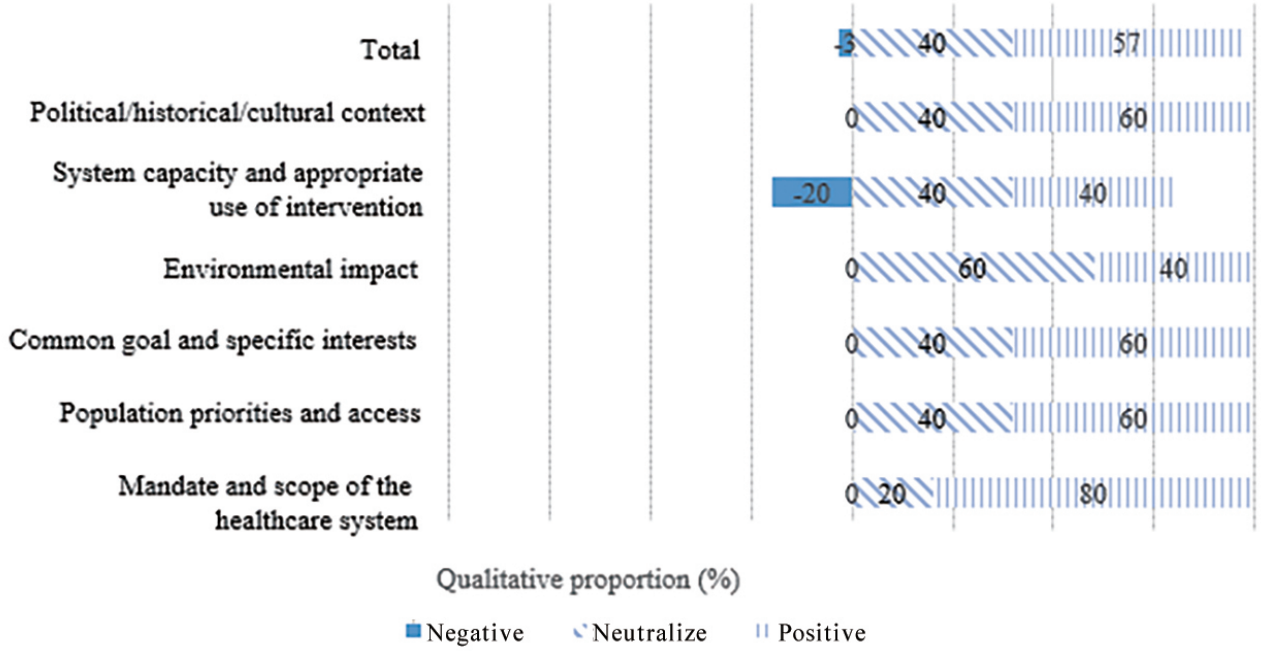

Fig. 5 Results of qualitative analysis of siltuximab

5 Uncertainty analysis

The evaluation results of MCDA were heterogeneous, and each operational step in its evaluation process may be a source of uncertainty, and the main certainties include: (1) Uncertainty in MCDA model settings and parameter inputs, such as parameters for indicator settings, evidence matrices, ratings and weighting or weighting of weight indicators; (2) Uncertainty in model parameters, such as differences in perceptions of ratings and weights; (3) Method uncertainty, such as weight calculation methods; (4) Uncertainty in evidence judgment, such as weight calculation relying on participants' subjective perceptions and experts' opinions since scoring; (5) Random uncertainty which was caused by random or unexplained variation.

The trend of MCDA evaluation results with uncertainty could be explored by applying uncertainty analysis, and this paper explored the impact of parameter uncertainty and variability on the study results through deterministic sensitivity analysis. Deterministic sensitivity analysis allows the observation of changes in the contribution of a change in a parameter (indicator weight or score) to the value of the evaluated drug by changing one parameter at a time.

The results of the sensitivity analysis were obtained by reducing the weight of each indicator by 10% and increasing the weight of each indicator by 10%. The MCDA value of siltuximab changed significantly after changing the weights of the indicators of therapeutic benefit from the drug and drug effectiveness, which had higher weights, the deterministic sensitivity analysis of index weights is shown in Fig. 6.

The results of the sensitivity analysis were obtained by reducing the scores of each indicator by 15% and increasing the scores of each indicator by 15%. The MCDA value of siltuximab changed significantly after changing the weight values of the higher-weighted indicators of therapeutic benefit from the drug and drug effectiveness the deterministic sensitivity analysis of value score is shown in Fig. 7.

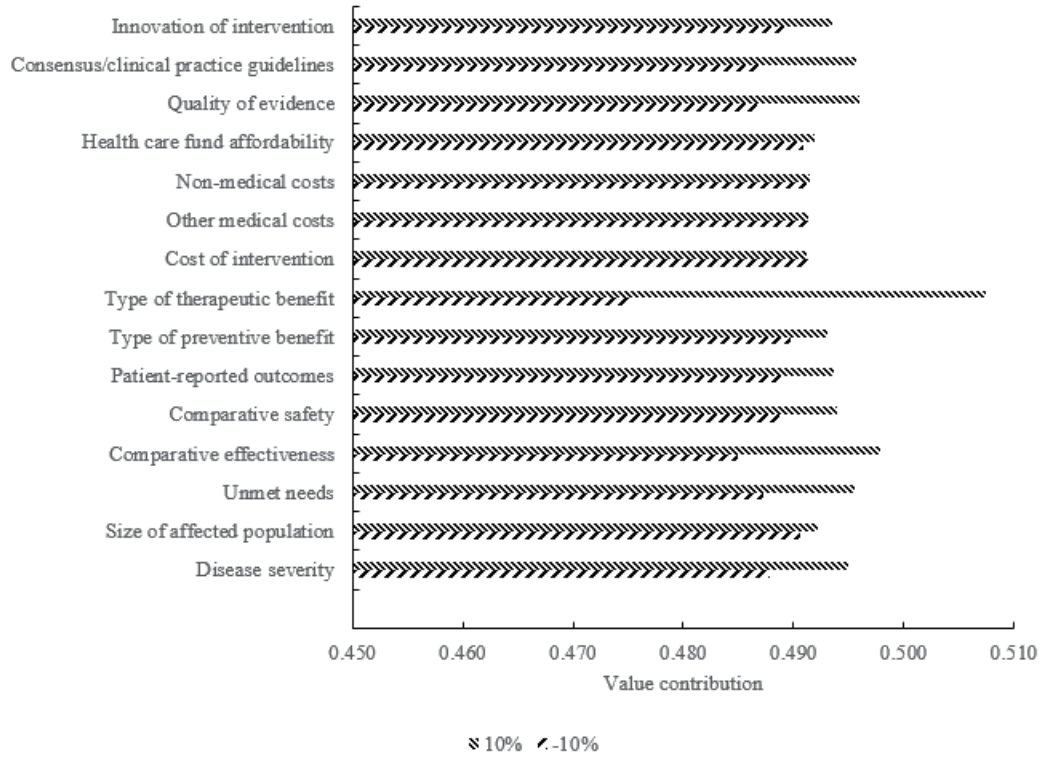

Fig. 6 Deterministic sensitivity analysis of index weights

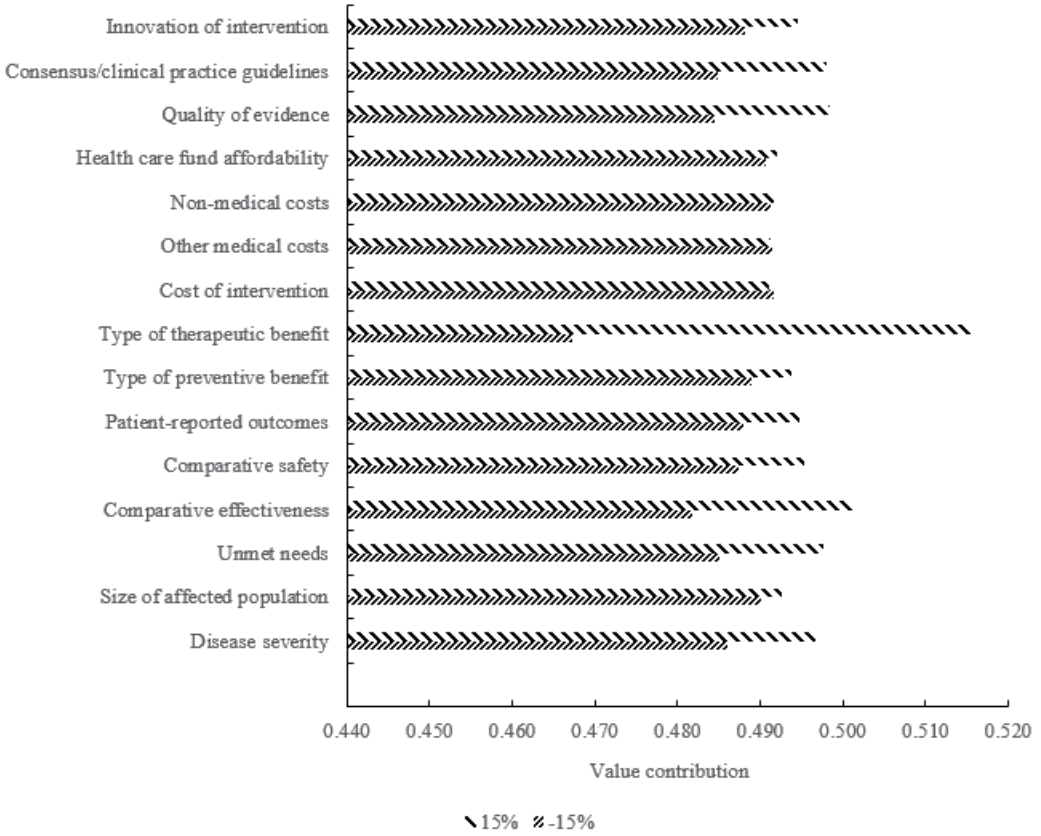

Fig. 7 Deterministic sensitivity analysis of value score

6 Conclusion

The value score for siltuximab was 0.491, and its treatment of Castleman disease had added value. Therapeutic benefits from the drug, drug effectiveness, and drug safety were the indicators of most concern to participants. Besides, experts' scores of all three indicators were more than 3. The value score for the five indicators such as drug effectiveness, drug safety, patient-reported outcomes, therapeutic benefit from the drug, and non-medical costs was 0.276, accounting for 56% of the total value score. Participants considered these indicators to be more valuable among the comparative indicators, under which siltuximab for Castleman disease was considered a more valuable treatment option. The indicator that negatively impacted the clinical value of siltuximab was cost of drugs. In the qualitative analysis of the scenario-based guidelines, 57% of the experts considered siltuximab to be a valuable treatment option.

As the first anti-IL-6 targeted monoclonal antibody approved in China, the launch of siltuximab fills the gap in the treatment of iMCD. Compared to other first-line treatment options previously used by iMCD patients, siltuximab is a more expensive drug, but experts also believe that it may have some potential savings in terms of non-medical costs.

7 Research limitations

The most significant limitation of this study is the small number of experts, MCD patients, business representatives, and public representatives in the first phase of the questionnaire, who have differences in their understanding of the indicators. The subjective differences of the participants may also have an impact on the assessment results.

As clinical evidence is used as an important part of the assessment, its quantity and quality will directly affect the expert's assessment of medical products. Due to the high cost of OMPs and difficulty in obtaining clinical evidence, the limited MCD-related evidence, and the absence of clinical trials related to other first-line treatment options for MCD, we can only carry out some indirect comparisons. Besides, the limited MCD-related clinical evidence in China most of the clinical evidence from foreign patients, and the direct application of their trial findings to the assessment of China's MCD patients will have an impact on the results of this study.

The contents of the questionnaires in this study are derived from the evidence matrix formed from literature studies. Because of the small number of rare disease-related studies, the year of publication of research literature and the time span of literature studies varying greatly, the evidence matrix required for the assessment of OMPs may have missing contents and discrepancies between the findings of previous studies and the actual ones, which can affect the experts' comprehensive understanding and their assessment of OMPs. In addition, compared to other first-line treatment options that have been in use for a long time, siltuximab is an innovative drug that has been on the market for a short time. Therefore, experts may lack clinical experience with siltuximab and they are likely to be influenced by previous experience in their assessment.

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