Cost-utility Analysis of R-CHOP vs CHOP in Patients with Non-Hodgkin's Lymphoma: A Systematic Review

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ABSTRACT

Background and Objectives. Non-Hodgkin Lymphoma (NHL) ranks 11th in cancer incidence and mortality in the Philippines with the combination chemotherapy composed of Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) being commonly used as treatment. However, the addition of Rituximab to CHOP (R-CHOP) has been shown to exhibit higher response rates and longer remissions, potentially improving quality of life. Currently, there is conflicting evidence on the cost-utility of CHOP versus R-CHOP. The study aimed to describe the patient- and country-specific factors, and treatment modalities used for NHL and systematically review cost-utility evidence of R-CHOP versus CHOP in adult NHL patients.

Methods. A systematic literature search of cost-utility studies on R-CHOP versus CHOP for NHL treatment was performed on eight databases: PubMed/MEDLINE, Scopus, Web of Science, EBSCOHost, Cochrane, York Research Database, Centre for Reviews and Dissemination Database, and HERDIN, where 607 studies were identified. Upon screening using an eligibility criteria, 10 studies were included and critically assessed using four appraisal tools: CHEERS, Drummond, Cooper, and ECOBIAS. These were performed independently by two authors with a third author assisting to help reach a consensus.

Results. All studies from high-income countries (HICs) (n=8) and low-middle-income country (LMIC) (n=1) suggested that R-CHOP was more cost-effective for NHL treatment than CHOP in terms of utility outcomes. The study conducted in a low-income country (LIC) (n=1) suggested the opposite, favoring CHOP over R-CHOP. Methodological differences such as perspective, discount rate, willingness-to-pay (WTP), time horizon, and economic model were observed. Methodological limitations include completeness of data reported and credibility of sources used.

Conclusion. The results of this review shall be interpreted with caution as those favoring R-CHOP over CHOP for NHL treatment in terms of cost-utility were concentrated in HICs. More economic evaluations from LICs, LMICs, and upper-middle income countries (UMICs) are needed for a robust conclusion. Additionally, establishing a universally recognized guideline for economic evaluations is essential to guide researchers effectively.

Keywords: Non-Hodgkin's Lymphoma, R-CHOP, CHOP, Rituximab, cost-utility, economic evaluation

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INTRODUCTION

Background

Lymphoma is a group of heterogeneous malignancies arising from the lymphatic system and is characterized by the abnormal proliferation of lymphocytes or their precursor cells.[1] According to the morphology, immunophenotype, genetic, molecular, and clinical features, the two broad classifications of lymphoma are Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL). HL is characterized

by the presence of the Reed-Sternberg (RS) cells while NHL primarily affects mature and precursor B- and T-cells and does not consist of RS cells.[2]

NHL remains one of the most common cancer types in the United States making up approximately 4% of all cancer cases with about 85% accounting for the B-cell subtype.[3] The American Cancer Society estimates that in 2023, around 80,550 people, including both adults and children, will be diagnosed with NHL. Additionally, it is estimated that approximately 20,180 fatalities will result from this cancer type. The risk for NHL is higher in males than in females. For males, there is a 1-in-43 chance to develop NHL in their lifetime compared to a 1-in-53 chance for females. Though NHL can occur at any age, the risk of developing NHL increases with age. It is most common in the elderly, particularly those aged 65 to 74 years, with a median age of 67.[2,4]

In the Philippines, NHL is the 11th most common form of cancer. In 2022, around 4,989 cases, which makes up around 2.6% of the overall total number of cancer cases, were attributable to NHL. Further, 2,876 deaths (2.5%) out of all cancer-related deaths in the same year were also attributed to NHL, making it the 11th most common cause of cancer-related deaths.[5]

CHOP is a first-generation, combination chemotherapy regimen composed of Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. It has been considered as standard therapy in patients with advanced stages of intermediate-grade or high-grade NHL based on numerous clinical studies where second and third-generation chemotherapy regimens failed to prove an advantage.[6,7] This treatment regimen is administered with an average treatment cycle lasting for 21 days (3 weeks) and patients can receive six to eight cycles in total, depending on the type and stage of NHL.[8]

However, subsequent randomized trials have demonstrated that both aggressive and indolent NHL subtypes benefit from the addition of Rituximab to first-line treatment (R-CHOP) in terms of overall survival.[8] Rituximab is the first targeted therapy for lymphoma that has significantly contributed to major breakthroughs in the prognosis of NHL and has been widely incorporated into treatment guidelines such as in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for NHL and ESMO Clinical Practice Guidelines for diffuse large B-cell lymphoma.[9,10] Three to six cycles of R-CHOP may be administered to patients with stage 1 or stage 2 NHL, with radiation therapy occasionally performed afterward while patients in stages 3 or 4 may receive six chemotherapy sessions. Even though the addition of Rituximab to CHOP has been shown in randomized trials to improve overall survival, the CHOP regimen is still mostly used as the first-line treatment for NHL in the Philippines while the addition of Rituximab to standard chemotherapy is mostly regarded as a second-line option.[11-13]

The mechanism of action of the CHOP regimen that enables this combination therapy to potentially cure NHL is based on the individual mechanism of action of its components: Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone. Cyclophosphamide is an alkylating agent that damages and blocks the production of the DNA of cancer cells, while Doxorubicin is an anthracycline topoisomerase inhibitor that disrupts topoisomerase-II-mediated DNA repair by intercalating into the cell's DNA.[14,15] Vincristine, on the other hand, is an antitumor alkaloid that prevents cell division by prohibiting microtubule polymerization during mitosis, while Prednisone is a steroid that exerts its anti-inflammatory, immunosuppressive, and vasoconstrictive effects by binding to intracellular receptors, which then influences the target tissues' gene transcription.[16-18] The addition of Rituximab to CHOP therapy, through its chimeric nature, allows for more effective utilization of the body's complement- and cell-mediated lysis mechanism (immune-mobilizing effects) in addition to its direct cytotoxic effects. Further, the addition of Rituximab also allows for more cell-specific cytotoxic action since it specifically binds to CD20 receptors which are commonly present in the B-cell lineage and in over 95% of B-cell lymphomas.[19,20]

Evidence of the cost-utility of R-CHOP compared to CHOP among countries of different World Bank income classifications is somewhat contradictory. Among HICs, R-CHOP is more cost-effective than CHOP in treating patients with different types and stages of NHL in terms of utility measures.[21-26] This is congruent with various clinical practice guidelines (CPGs) from these countries such as the National Institute for Health and Care Excellence (NICE) Guidelines and NCCN Guidelines which place Rituximab-chemotherapy combination as first-line treatment for NHL.[27,28] Meanwhile, there is a scarcity of economic evaluation in LICs, LMICs, and UMICs. However, a study from Indonesia, currently an UMIC but an LMIC during the year of the study, suggests that R-CHOP is also more cost-effective than CHOP in treating patients with NHL in terms of utility measures.[29] The economic evidence from HICs and LMICs on the cost-utility of R-CHOP versus CHOP is contradictory to a study conducted in Malawi, an LIC, which stated that CHOP is more cost-effective than R-CHOP.[30] At present, there is no recent (≤10 years) systematic review on the cost-utility of R-CHOP versus CHOP that can synthesize and settle the incongruence between studies from countries of different income classifications. A new systematic review of the available evidence is needed since there has been an increase in the number of economic evaluations published since the last systematic review found.[31] Hence, it is necessary to systematically review such evidence again to take into account the most recent data available that may help in determining which intervention is more cost-effective. This study can potentially be used as a basis on whether the addition of Rituximab to chemotherapy should be prioritized in CPGs, formularies, and health packages for NHL treatment.

Considering this, it was deemed necessary to perform a systematic review of available cost-utility analyses of R-CHOP and CHOP regimens in adult patients with NHL to synthesize available data and determine whether R-CHOP is more cost-effective in terms of utility measures and cost-utility outcomes. This may potentially address conflicting evidence regarding the cost-effectiveness of R-CHOP between HICs, LICs, and LMICs. This may also highlight potential reasons why R-CHOP regimens should be prioritized in the treatment of adult patients with NHL.

This study aims to review the cost-utility of R-CHOP as compared to CHOP in adult patients with NHL. Specifically, the study aims to: (1) describe the patient- and country-specific factors as well as the treatment modalities used for patients with NHL; and (2) systematically review evidence of costs, utilities, and cost-utility of patients with NHL treated with either R-CHOP and CHOP. The results of this study may supply necessary evidence to inform policy and clinical decision-makers in support of the inclusion of Rituximab in formularies, treatment packages covered by national insurance, and CPGs for treating NHL.

MATERIALS AND METHODS

Study Design

A systematic review of existing literature on CHOP and R-CHOP and its cost-utility on adult patients with NHL was performed. The review protocol was registered and can be publicly accessed in the International Prospective Register of Systematic Reviews (PROSPERO) with identification number of CRD42023483304. This is to avoid possible duplication of study, allow comparison of review methods against other available registered studies, and ensure reproducibility of the study protocol. The 2022 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was used to ensure the completeness of the data reported in this review. The following processes were performed by two independent authors with a third author helping reach a consensus. The study was implemented throughout a period of nine months from October 2023 to June 2024. Meta-analysis was not performed due to insufficiency of data. Aside from the non-completion of the meta-analysis portion of this study, there were no other deviations from protocol.

Search Strategy

An exhaustive literature search involving eight databases was performed by two independent authors. The databases searched include PubMed/MEDLINE, Scopus, Web of Science, EBSCOHost, Cochrane Library, York Research Database, the University of York Centre for Reviews and Dissemination Database, and HERDIN. To have a comprehensive review of literature, grey literature, and local and international clinical practice guidelines were also assessed. This was done primarily by visiting the National Library of the Philippines and the libraries found in various colleges of UP Manila to search for relevant studies which may be included in this systematic review. As search databases have different Boolean operators, different search strings were created. Notably, other search terms such as specific NHL subtypes (i.e., DLBCL, FL) were used but yielded results that were too specific and did not satisfy the PICO, thus a more general search strategy was implemented instead. The following keywords, as shown in Appendix A, were used. Search results were then collated in Google Sheets.

Eligibility Criteria

This study underwent initial screening independently by two authors and the results were discussed by the authors until a consensus was reached. A third author was asked to help resolve any disagreements. Studies and articles were deemed eligible based on the following criteria: (1) adult patients (≥18 years old) with NHL treated with CHOP with or without Rituximab; and (2) includes utility measures such as health-related quality of life (hrQoL), quality-adjusted life years (QALY), and disability-adjusted life years (DALY) or cost-utility outcomes such as incremental cost-utility ratio (ICUR) and incremental net benefit (INB). Studies were considered for eligibility regardless of language but only studies published from November 1997 to September 2023 were considered in line with the introduction of Rituximab to the market in 1997.[32] Studies were deemed ineligible based on the following exclusion criteria: (1) not relevant to population, intervention, comparator, and outcomes (PICO) of interest; (2) not an original article; and (3) duplicates.

After the initial screening, full-text articles were retrieved and reviewed based on the PICO of interest. The authors used the Screening Eligibility Form found in Appendix B during the initial and full-text screening to ensure standardization of decisions made by the authors and to keep track of the studies they reviewed.

Methodological Assessment

The methodological assessment was composed of critical appraisal and risk of bias assessment of the included studies. The included studies were appraised using appropriate appraisal tools to ensure the inclusion of high-quality data and minimize the risk of bias. Four critical appraisal tools were used to assess the quality of the included studies in this systematic review: (1) the 2022 CHEERS checklist; (2) Cooper's Potential Hierarchies of Data Sources; (3) Drummond's Checklist; and (4) the Bias in Economic Evaluation (ECOBIAS). The first three checklists were used to critically appraise the quality of the studies while the presence of risks of bias was assessed using the fourth checklist.

The 2022 CHEERS checklist was used in order to know the minimum amount of data health economic evaluations must report. A maximum score of 28 was regarded as full reporting compliance for this economic evaluation.[33] The

study also made use of Cooper's Potential Hierarchies of Data Sources which ranks the appropriateness of the use of particular study designs depending on the data component of interest. Based on the value of the score, the quality of input data was then categorized as high (1–2), medium (3–4), or low (5–6).[34] Further, the study utilized Drummond's checklist which assesses the validity of the results of an economic evaluation study. Each item is rated as derived on a scale developed by Doran, where a potential score of 1 is assigned to each. The total score categorizes the economic quality as poor (30%), average (31–70%), or good (>70%).[35] The ECOBIAS checklist focuses specifically on providing an overview of the possible biases that could be present in economic evaluations. Thus, the ECOBIAS checklist was used to assess the possible risks of bias in the studies to be included.[36]

Reporting Format

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) was used to present the flow of the systematic review that was performed. A PRISMA flow diagram was created to show the number of records identified, included, excluded, and the reasons for exclusion.

Data Extraction

Data extraction was performed by two independent authors using the Data Extraction Form found in Appendix C. The data extracted was based on the following domains: (1) general information, (2) study-specific characteristics, (3) participant characteristics, (4) intervention and comparators, (5) outcomes measures, (6) sensitivity analysis, and (7) data for quantitative analysis. Any missing data from the studies were tagged as unreported and were accounted for in the critical appraisal of the studies.

Data Analysis

The characteristics of all included studies were analyzed using frequency statistics and presented through a narrative summary of the evidence in both text and tabular forms.

Ethical Considerations

The study was registered with the UPM Research Grants Administration Office (RGAO) and was submitted to the University of the Philippines Manila Research Ethics Board (UPMREB) for review and ethical approval (UPMREB 2023-0306-01). Any suggestions and recommendations from the UPMREB Panel were complied with by implementing appropriate revisions to the protocol to ensure ethical soundness until it was satisfactory to the panel.

RESULTS

An exhaustive literature search was done using the search strategy for each database as shown in Appendix D. After screening of titles and abstracts, a total of nineteen studies were attained. From this number, nine were excluded from the review for the following reasons: one was not relevant to the intervention of interest; one was not relevant to the outcomes of interest; three did not have cost-utility designs; and four were not original articles. The PRISMA flow diagram is shown in Figure 1. The remaining ten cost-utility analyses eligible for qualitative synthesis were conducted in nine different countries (Canada = 1; Finland = 1; France = 1; Indonesia = 1; Italy = 1; Malawi = 1; Netherlands = 1; United Kingdom = 2; United States of America = 1).

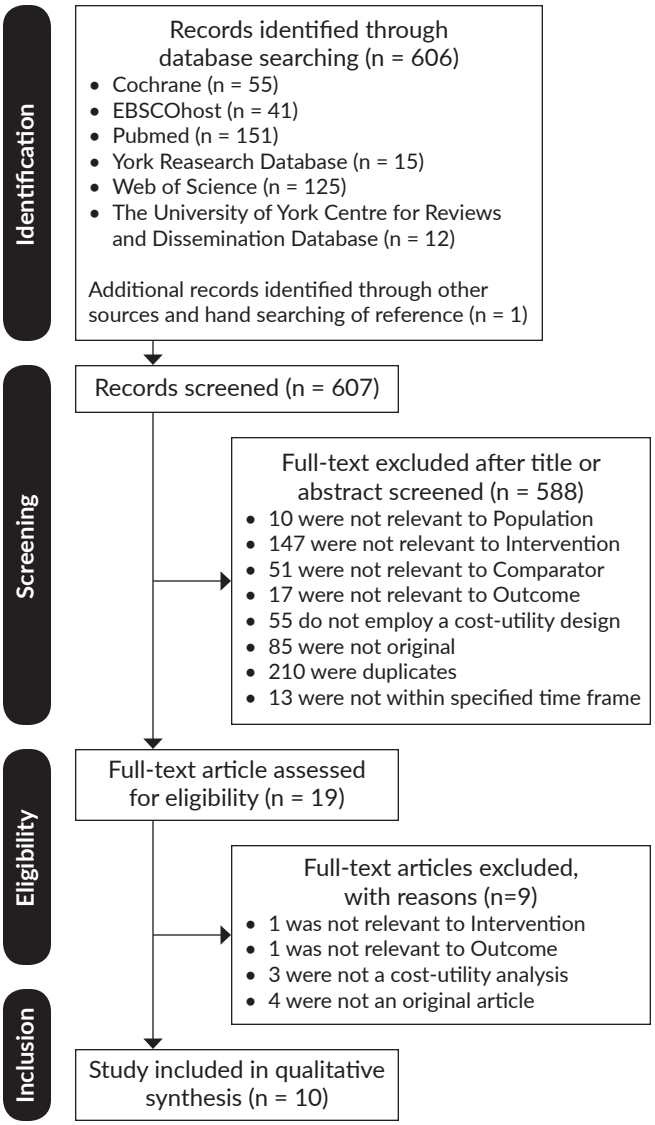

Figure 1. PRISMA flowchart of literature search and assessment.

Study Characteristics

The summary of the characteristics of the included studies is shown in Table 1. Of the ten included studies, only two studies (20%) were recently published within the past 10 years while the remaining eight studies (80%) were published

Table 1. Summary of the Characteristics of Included Studies

Item	Frequency (%)
General Information	
First Author Affiliation	
HIC	8 (80)
LMIC	1 (10)
LIC	1 (10)
Publication Year	
2013 to 2023	2 (20)
2003 to 2012	8 (80)
Publication Journal	
International	10 (100)
Funding	
Government	3 (30)
Private	5 (50)
Mixed funding	1 (10)
Not stated	1 (10)
Conflict of Interest (COI)	
Reported	4 (40)
With COI	1 (10)
Without COI	3 (30)
Not reported	6 (60)
Patient-specific Characteristics	
Population	
DLBCL	8 (80)
FL	2 (20)
Staging	
II + III + IV	5 (50)
Not reported	5 (50)
Treatment Status	
Naive	7 (70)
Relapsed + Refractory + Remission	2 (20)
Not reported	1 (10)
Other Treatment Regimens	
R-CHOP vs CHOP only	9 (90)
R-(CHOP vs CVP vs CHVP vs MCP) vs chemotherapy alone	1 (10)
Cycle	
6	4 (40)
8	5 (50)
Not reported	1 (10)
Outcomes	
Clinical outcomes	
OS	6 (60)
DFS	4 (40)
PFS	4 (40)
PPS	4 (40)
EFS	2 (20)
Non-disease-free survival	1 (10)
YLL	1 (10)
Death	1 (10)
LYG	4 (40)
Humanistic outcomes	
QALY	9 (90)
DALY	1 (10)
Sample Size	
Reported	5 (50)
Not Reported	5 (50)

Item	Frequency (%)
Country	
Africa	1 (10)
America	2 (20)
South-East Asia	1 (10)
Europe	6 (60)
Country Income Level	
HIC	8 (80)
LMIC	1 (10)
LIC	1 (10)
Study Design	
CUA	8 (80)
CUA with BIA	1 (10)
CUA with SR	1 (10)
Study Perspective	
Societal	4 (40)
Payer	5 (50)
Not mentioned	1 (10)
Discount Rate	
Costs	
3%	6 (60)
3.5%	1 (10)
4%	1 (10)
6%	2 (20)
Utilities	
1.5%	2 (20)
3%	6 (60)
3.5%	1 (10)
4%	1 (10)
Currency	
US Dollar	3 (30)
Canadian Dollar	1 (10)
Euro	4 (40)
Pound	2 (20)
Model Type	
Markov	7 (70)
Decision tree	1 (10)
Microsimulation	1 (10)
Unnamed	1 (10)
Time horizon	
5 years	1 (10)
15 years	5 (50)
Lifetime	4 (40)
Costs	
Direct medical only	8 (80)
Direct medical + nonmedical	1 (10)
Direct medical + nonmedical + indirect	1 (10)
Sensitivity analysis	
One-way sensitivity analysis + Multi-way sensitivity analysis	1 (10)
One-way sensitivity analysis + Expected value of perfect information + Threshold analysis + Probabilistic sensitivity analysis	5 (50)
One-way sensitivity analysis + Probabilistic sensitivity analysis	1 (10)
One-way sensitivity analysis + Subgroup analysis + Probabilistic sensitivity analysis	1 (10)
One-way sensitivity analysis + Scenario analysis + Probabilistic sensitivity analysis	1 (10)

HIC – High-Income Countries, LMIC – Low-Middle-Income Countries, LIC – Low-Income Countries, DLBCL – Diffuse Large B Cell Lymphoma, FL – Follicular Lymphoma, CHOP – Cyclophosphamide + Doxorubicin + Vincristine + Prednisone, CVP – Cyclophosphamide + Vincristine + Prednisone, CHVP – Cyclophosphamide + Doxorubicin + Tenoposide + Prednisone, MCP – Mitoxantrone + Chlorambucil + Prednisolone, OS – Overall Survival, DFS – Disease-Free Survival, PFS – Progression-Free Survival, PPS – Post-Progression Survival, EFS – Event-Free Survival, YLL – Years Life Lost, LYG – Life-Years Gained, QALY – Quality-Adjusted Life Year, DALY – Disability-Adjusted Life Year, CUA – Cost-Utility Analysis, BIA – Budget Impact Analysis, SR – Systematic Review

before 2013.[21-23,25,26,29,30,37-39] Eight authors in the included studies were based in HICs (80%), one in LMIC (10%), and one in LIC (10%).[21-23,25,26,29,30,37-39] All included studies were internationally published (100%) with various sources of funding and more than five (50%) of the studies were sponsored by private companies. Conflict of interest was only reported in four (40%) of the included studies.[23,26,29,30] In one of these studies (10%), Painschab et al. stated that competing interests in three of its authors were present due to their concurrent financial grants.[30] Detailed general characteristics of the included studies can be found in Appendix E.

Patient-specific Information

Age and Sex

The mean age of these patients is 54.5 ± 6.61 years old as reported by four studies.[21,25,29,30] The other four studies divided their patients into two groups based on their age: (1) patients younger than 60 years old; and (2) patients 60 years old and older.[23,37-39] Meanwhile, the remaining two studies did not report the age of their patients.[22,26] None of the included studies reported the sex of their patients.

Type and Stage of NHL and Treatment Status

Eight studies included patients with DLBCL while the remaining two studies included patients with FL.[21-23,25,26,29,30,37-39] Five studies reported the NHL staging of the patients, which was Stage II, III, and IV.[21-23,37,39] Seven studies only included patients who were treatment-naive while the other two studies included patients whose treatment status were relapsed, refractory, or remission.[21-23,26,29,30,37-39] On the other hand, Ray et al. did not report the treatment status of their patients.[25]

Treatment Regimen

The CHOP regimen was composed of intravenous Cyclophosphamide 750 mg/m^2 given on Day 1, intravenous Doxorubicin 50 mg/m^2 given on Day 1, intravenous Vincristine 1.4 mg/m^2 given on Day 1, and oral Prednisone 40 mg/m^2,60 mg/m^2, or 100 mg/m^2 given on Days 1 to 5, with a 3-week interval for 6 to 8 weeks. For the dose of Prednisone, six studies used Prednisone 40 mg/m^2, one study used Prednisone 60 mg/m^2, two studies used Prednisone 100 mg/m^2, while one study did not report any dose.[21-23,25,26,29,30,37-39] For the number of cycles used, four studies reported using 6 cycles of CHOP, five studies used 8 cycles, while one study did not report any cycle.[21-23,25,26,29,30,37-39] For patients under the R-CHOP regimen, the same regimen for CHOP as discussed above was used by the included studies. The only difference was the addition of intravenous Rituximab 375 mg/m^2 on Day 1, given at a 3-week interval.

In one of the included studies, Rituximab was added to different chemotherapy regimens other than CHOP, including MCP (Mitoxantrone, Chlorambucil, and Prednisolone), CVP (Cyclophosphamide, Vincristine, Prednisone), and CHVP+IFNα (Cyclophosphamide, Etoposide, Doxorubicin, Prednisolone, Interferon-alpha) and was compared to chemotherapy alone.[25]

Outcomes

The reported outcomes of the included studies were limited to clinical and humanistic outcomes. For clinical outcomes, the majority of the included studies reported the overall survival (OS) of their participants.[21-23,29,37,39] However, the included studies differ in their reported surrogate outcomes. Disease-free survival (DFS), progression-free survival (PFS), and post-progression survival (PPS) were the most common surrogate outcomes reported by the studies. Specifically, four studies reported DFS, PFS, PPS, and LYG.[21,23,25,26,29,37-39] Other surrogate outcomes include event-free survival (EFS) which was reported by two studies, non-disease-free survival reported by Best et al., and years of life lost and death reported by Painschab et al.[21,22,29,30] For humanistic outcomes, nine out of ten studies used QALY as their main outcome measure while only one study used DALY.[21-23,25,26,29,30,37-39]

Country-specific Information

Shown in Appendix F are the country- and study-specific information of the included studies.

Country and Country Income Classification

The included studies were categorized based on their country setting using the WHO region classification. The majority of the studies were conducted in the European Region (EUR) (60%), followed by the Region of the Americas (AMR) (20%), and then the South-East Asian Region (SEAR) (10%) and African Region (AFR) (10%). The majority of the studies were based in HICs (80%). Only one study was conducted in an LMIC (10%) and an LIC (10%).[29,30] The study of Putri et al. was conducted in Indonesia, an LMIC during the year the economic evaluation was undertaken but a UMIC during the year of this review.[29]

WTP Threshold

In terms of the WTP threshold, two studies (20%) utilized a WTP threshold equivalent to three times the GDP of their respective countries.[29,30] Putri et al. also used a WTP threshold equivalent to one times the GDP of Indonesia.[29] Three studies (30%), on the other hand, had established WTP thresholds tailored to their specific studies.[23,25,38] Notably, five studies (50%) did not specify a WTP threshold.[21,22,26,37,39]

Study-specific Information

Study Design

All studies employed a model-based CUA study design. Furthermore, Berto et al. also conducted a budget impact analysis (BIA) subsequent to their CUA, which is usually performed when an intervention is deemed cost-effective.[39]

Meanwhile, Knight et al. added an economic evaluation in the form of CUA on top of its systematic review on the use of Rituximab in aggressive NHL.[23]

Study Perspective

The studies have been grouped into two broad categories based on Sittimart et al.: payer perspective and societal perspective.[40] Five studies adopted a healthcare payer perspective focusing their analysis on expenses incurred and outcomes obtained from the perspective of healthcare payers, such as insurance companies or government healthcare programs.[21,25,26,30,39] Four studies adopted a societal approach, which involves a thorough evaluation of costs and outcomes that go beyond the healthcare industry to incorporate societal outcomes and costs such as direct non-medical, indirect, and spillover costs affecting other sectors besides health such as education.[22,23,29,37] Lastly, one study did not explicitly specify the study perspective they utilized.[38]

Discount Rate

The majority of the studies (60%) employed a 3% discount rate for both costs and utilities, irrespective of the country's income classification.[21,22,26,29,30,38] However, two studies conducted in HICs utilized discount rates of 6% and 1.5% for costs and utilities, respectively.[23,39] Notable variations include Groot et al. from the Netherlands, who applied a 4% discount rate for both costs and utilities, and Ray et al. from the UK, who employed a 3.5% discount rate for both costs and utilities.[25,37]

Model and Time Horizon

Three studies made use of a Markov state-transition model with three health states: progression-free (PF), progression (PD), and death (D).[25,26,29] The time horizon for these studies covered a patient's lifetime.

Knight et al. applied a Markov state-transition model with three health states split into two age cohorts, patients aged ≥60 years and <60 years.[23] Here, the three health states used in this study were: (1) complete responder (CR) to treatment, (2) non-responder and relapse from complete responders (NR), and (3) death. Effectiveness and cost were evaluated over a 15-year time horizon.

The economic analysis by Groot et al. implemented a Markov-state transition model with six health states with distinction between patients aged ≥60 years and <60 years.[37] In their model, patients start with the initiation of treatment. From there, there are two possible outcomes: (1) a complete response and (2) no complete response. Complete responders are further comprised of those who are complete responders and unconfirmed complete responders. From there patients may progress to second-line treatment and/or death. The outcomes of this study were evaluated over a 15-year time horizon.

Two economic evaluations used a Markov Model with five health states to predict the sequence of treatments, outcomes, and costs of patients receiving CHOP with or without Rituximab over a time horizon of 5 years.[22,37] For Hornberger and Best, the health states used were: (1) event-free where patients were assumed to start treatment with CHOP with or without Rituximab, (2) salvage, (3) transplantation, (4) end-of-life care, and (5) death. On the other hand, Berto et al.'s five health states included the following: (1) start treatment, (2) complete response, (3) no response, (4) progression, and (5) death. The former study evaluated outcomes over a duration of 5-years while the latter covered 15-years.

Only one study developed a three-strategy decision-tree model comparing best supportive care, CHOP, and R-CHOP.[30] The first chance node separated patients who achieved remission and those who had refractory disease or treatment-related mortality. Those in remission were further separated by a second chance node to those who relapsed after remission and those who maintained remission at 2 years. Those who achieved 2-year progression-free survival were considered DLBCL-free. Finally, all the patients who relapsed were assumed to enter palliative care since treatment with curative intent post-relapse was not available in the setting of the analysis.

A microsimulation model was used to compare CHOP and R-CHOP as first-line therapy in the economic evaluation performed by Johnston et al.[38] Separate evaluations were done for CHOP and R-CHOP, and for patients who are aged ≥60 years and <60 years. In this model, patients start their treatment. Those patients surviving past treatment periods were assigned to two outcomes, eventual DLBCL relapse or eventual mortality from non-DLBCL causes with no prior relapse. Patients assigned to the relapse group were then randomly assigned to three second-line treatment regimens: (1) second-line chemotherapy alone, (2) high-dose second-line chemotherapy plus stem-cell transplantation, or (3) palliative care. Time until death was randomly generated for each individual in this model. A time horizon of 15 years was used.

Finally, Best et al. developed a model to compare the CHOP and R-CHOP.[21] Their model was applied to patients aged 60 to 80 years old with untreated DLBCL stage II, III, or IV and a performance status of 0 to 2. A reference-case patient which was assumed to have the initial characteristics of the average patient enrolled in the LNH 98-5 study was also used in their model. A 15-year time horizon was used for Best et al.'s analysis.

Results of Economic Evaluations

Shown in Table 2 are the costs, utilities, and cost-utility outcomes of the included studies.

Costs and Resource Use

The majority of the studies (60%) performed a retrospective data collection of costs with the use of different kinds of evidence.[22,25,26,30,37,38] Three studies (30%) utilized both prospective and retrospective data to account for the costs

Table 2. Costs, Utilities, and ICURs of Included Studies

Study	Total Costs			Utilities			ICUR
	Method of data collection	CHOP	R-CHOP	Method of data collection	CHOP	R-CHOP	
Europe							
Berto et al., 2004	Prospective & retrospective	<60 y/o: €4,589.00 ≥60 y/o: €7,450.00	<60 y/o: €19,427.00 ≥60 y/o: €21,388.00	Prospective	<60y/o: 5.77 QALY ≥60y/o: 3.08 QALY	<60y/o: 6.81 QALY ≥60y/o: 4.23 QALY	<60y/o: €13,362.00/QALY ≥60y/o: €12,879.00/QALY
Knight et al., 2004	Prospective & retrospective	<60 y/o: £7,311.00 ≥60 y/o: £5,773.00	<60 y/o: £15,181.00 ≥60 y/o: £14,456.00	Retrospective	<60 y/o: 6.10 QALY ≥60 y/o: 3.77 QALY	<60 y/o: 7.15 QALY ≥60 y/o: 4.58 QALY	<60 y/o: £7,533.00/QALY ≥60 y/o: £10,596.00/QALY
Best et al., 2005	Prospective	€28,782.00	€41,952.00	Retrospective	Undiscounted: 4.17 QALY Discounted: 3.59 QALY	Undiscounted: 5.45 QALY Discounted: 4.66 QALY	4-yr: €29,976.00/QALY 15-yr: €12,259.00/QALY
Groot et al., 2005	Retrospective	Undiscounted: <60 y/o: €28,954.00 ≥60 y/o: €27,754.00 Discounted: <60 y/o: €27,828.00 ≥60 y/o: €26,891.00	Undiscounted: <60 y/o: €41,425.00 ≥60 y/o: €43,850.00 Discounted: <60 y/o: €40,171.00 ≥60 y/o: €42,751.00	Retrospective	Undiscounted: <60 y/o: 6.59 QALY ≥60 y/o: 3.61 QALY Discounted: <60 y/o: 5.19 QALY ≥60 y/o: 2.98 QALY	Undiscounted: <60 y/o: 7.74 QALY ≥60 y/o: 4.72 QALY Discounted: <60 y/o: 6.07 QALY ≥60 y/o: 3.87 QALY	Undiscounted: <60 y/o: €10,906.00/QALY ≥60 y/o: €14,499.00/QALY Discounted: <60 y/o: €13,983.00/QALY ≥60 y/o: €17,933.00/QALY
Ray et al., 2010	Retrospective	£20,922.00	£29,794.00	Retrospective	5.504 QALY	6.335 QALY	£10,676.00/QALY
Soini et al., 2011	Retrospective	€49,562.00	€59.521.00	Retrospective	3.90 QALY	4.72 QALY	€12,123.00/QALY
America							
Hornberger & Best, 2005	Retrospective	$30,043.00	$42,777.00	Retrospective	2.11 QALY	2.77 QALY	$19,297.00/QALY
Johnston et al., 2010	Retrospective	Undiscounted (15-yr): <60 y/o: C$37,214.00 ≥60 y/o: C$35,373.00 Discounted (15-yr): <60 y/o: $36,765.00 ≥60 y/o: $34,968.00 Discounted (5-yr): <60 y/o: $36,623.00 ≥60 y/o: $34,948.00	Undiscounted (15-yr): <60 y/o: C$46,783.00 ≥60 y/o: C$43,139.00 Discounted (15-yr): <60 y/o: $46,337.00 ≥60 y/o: $42,892.00 Discounted (5-yr): <60 y/o: $46,287.00 ≥60 y/o: $42,881.00	Retrospective	Undiscounted (15-yr): <60 y/o: 7.7 QALY ≥60 y/o: 4.2 QALY Discounted (15-yr): <60 y/o: 6.4 QALY ≥60 y/o: 3.6 QALY Undiscounted (5-yr): ≥60 y/o: 4.2 QALY Discounted (5-yr): <60 y/o: 3.0 QALY ≥60 y/o: 2.0 QALY	Undiscounted (15-yr): <60 y/o: 8.3 QALY ≥60 y/o: 6.0 QALY Discounted (15-yr): <60 y/o: 6.9 QALY ≥60 y/o: 5.0 QALY Undiscounted (5-yr): ≥60 y/o: 6.0 QALY Discounted (5-yr): <60 y/o: 3.2 QALY ≥60 y/o: 2.4 QALY	Undiscounted (15-yr): <60 y/o: C$15,948.00/QALY ≥60 y/o: C$4,414.00/QALY Discounted (15-yr): <60 y/o: C$19,411.00/QALY ≥60 y/o: C$5,853.00/QALY Discounted (5-yr): <60 y/o: C$48,320.00/QALY ≥60 y/o: C$19,833.00/QALY
Africa							
Painschab et al., 2021	Retrospective	$1,776.00	$5,100.00	Prospective	Per Patient: 21.6 DALY Per Population: 13,587 DALY	Per Patient: 18.8 DALY Per Population: 11,825 DALY	$1,204.00/DALY
Southeast Asia							
Putri et al., 2022	Prospective & retrospective	$94,931.00	$105,847.00	Prospective	3.00 QALY	4.06 QALY	$9,280.00/QALY

of NHL treatment.[23,29,39] Lastly, only one study solely used prospective data in the estimation of costs in their study.[21]

For studies with a societal perspective, the costs reported were mostly direct medical costs which include chemotherapy costs, monitoring and follow-up costs, treatment costs for relapse or refractory, end-of-life care costs, and other unspecified direct medical costs.[22,23,29,37] One study was able to include in its assessment both direct nonmedical costs including transportation, meals, accommodation, or any spending outside hospital services and indirect costs including productivity losses.[29] For studies with a payer perspective,the costs reported were mostly direct medical costs which include chemotherapy costs, diagnostic costs, adverse event costs, monitoring and follow-up costs, treatment costs for relapse or refractory, end-of-life care costs, and other unspecified direct medical costs.[21,25,26,30,39] One study was able to report nonmedical costs, specifically, travel costs associated with direct medical costs.[26] Johnston et al. did not specify the perspective used in their study, however, the study only accounted for direct medical costs including chemotherapy costs and treatment costs for relapse or refractory.[38]

The total costs vary depending on the perspective, time horizon, and discount rate, among other factors.

For studies with a societal perspective, the total costs for the CHOP regimen in USD ranged from $30,043.00 to $94,931.00 while the total costs for R-CHOP ranged from $42,777.00 to $105,847.00.[22,23,29,37] Furthermore, the discounted total costs in Euro ranged from €26,891.00 to €27,828.00 for CHOP and from €40,171.00 to €42,751.00 for R-CHOP while the undiscounted total costs ranged from €27,754.00 to €28,954.00 for CHOP and from €41,425.00 to €43,850.00 for R-CHOP.[37] Lastly, the estimation of total costs in Pound ranged from £5,773.00 to £7,311.00 for CHOP and from £14,456.00 to £15,181.00 for R-CHOP.[23]

For studies with a payer perspective, the total costs in USD amounted to $1,776.00 for CHOP and $5,100.00 for R-CHOP.[21,25,26,30,39] For the estimation of total costs in Euro, the range for CHOP was €4,589.00 to €49,562.00 while the range for R-CHOP was €19,427.00 to €59,521.00.[21,26,39] Lastly, the total costs in Pound was estimated to be £20,922.00 for CHOP and £29,794.00 for R-CHOP.[25]

Utilities

Five (50%) out of 10 studies derived their utility values using the (EQ-5D, QLQ-C30), and Multidimensional Fatigue Inventory (MFI-20) instruments, following the methodology outlined in Doorduijn et al.[21,22,37-39,41] In contrast, Putri et al. and Soini et al. utilized the EQ-5D-5L instrument to collect utility data on quality of life directly from patients through interviews and published clinical data sources, respectively.[26,29]

Knight et al. and Ray et al. employed the EQ-5D instrument for utility assessment; however, Ray et al. acquired their utility values from a study involving a cohort of 222 patients with follicular NHL in the UK.[23,25] Lastly, Painschab et al. obtained utility values from two distinct clinical datasets: (1) a prospective cohort treated with CHOP, documented by Painschab et al., and (2) clinical trial data evaluating R-CHOP, as reported by Kimani et al.[30,42,43] In summary, this systematic review shows that for patients under 60 years, both CHOP and R-CHOP treatments result in higher QALY compared to older patients. Additionally, R-CHOP was associated with higher QALY than CHOP alone. Conversely, DALY is higher in patients receiving CHOP alone compared to R-CHOP. However, it is important to note that the finding indicating a higher DALY in patients receiving CHOP alone as opposed to R-CHOP stems solely from the study conducted by Painschab et al.[30]

Incremental Cost-Utility Ratio (ICUR)

All studies included in this review reported ICURs that were below their respective WTP thresholds except Painshab et al., which garnered an ICUR above their WTP threshold.[30] The reported ICURs vary depending on the time horizon, discount rate, and age group of the participants in each study.

In general, the discounted incremental costs per QALY in USD ($) ranged from $9,280.00/QALY to $19,297.00/QALY while in CAD (C$), the incremental costs per QALY ranged from C$5,853.00/QALY to C$48,320.00/QALY.[22,29] On the other hand, estimation of incremental costs per QALY in Euro (€) ranged from €12,123.00/QALY to €29,976.00/QALY and estimation in Pound (£) ranged from £7,533.00/QALY to £10,676.00/QALY.[21,23,25,26,37,39] The increment cost per DALY in USD is $1,204.00/DALY.[30]

For the two studies that reported undiscounted ICURs, the ICUR in Euro of patients aged 60 years below is €10,906.00/QALY and those aged 60 years and older is €14,499.00/QALY while the ICUR in CAD in patients aged 60 years below is C$15,948.00/QALY and those aged 60 years and older is C$4,414.00/QALY.[37,38]

The summary of the cost-utility of R-CHOP against CHOP according to the country income classification is shown in Table 3. Among HICs, R-CHOP was deemed as the more cost-effective option than CHOP in terms of utility outcomes. Particularly, these countries, which were concentrated in EUR and AMR, reported ICURs below their

Table 3. Cost-utility of R-CHOP vs CHOP according to Country Income Classification

Country Income Classification	Cost-utility
HIC EUR – Italy, UK, France, Netherlands, Finland AMR – US, Canada	R-CHOP > CHOP
LMIC SEAR – Indonesia	R-CHOP > CHOP
LIC AFR – Malawi	CHOP > R-CHOP

respective WTP thresholds. Along with this, the only LMIC included in the review also favored R-CHOP over CHOP. However, the results from the HICs and the LMIC are contradictory to the results from the only LIC in the review. In Malawi, Africa, R-CHOP was deemed inferior to CHOP in terms of cost-utility with an ICUR of $1,204.00/DALY, exceeding their WTP of $1,014.00/DALY (cost-effective) and $338.00/DALY (highly cost-effective).

Sensitivity Analyses

All ten studies included in this systematic review implemented sensitivity analyses to test the robustness of the results of their base case analysis. Five studies implemented both one-way and probabilistic sensitivity analysis.[21,25,26,37,38] One study implemented two sensitivity analyses consisting of one-way sensitivity analysis and multi-way sensitivity analysis.[39] On the other hand, two other evaluations implemented three types of sensitivity analysis which includes one-way and probabilistic sensitivity analysis with either subgroup analysis or scenario analysis.[22,30] The study by Knight et al. implemented four types of sensitivity analysis in their study namely, one-way sensitivity analysis, expected value of perfect information, threshold sensitivity analysis, and probabilistic sensitivity analysis.[23] Finally, one study only performed a probabilistic sensitivity analysis on their base case results.[29]

Time horizon was the commonly reported variable that was most influential in the one-way sensitivity analysis performed. Despite this, ICURs were still reported to remain within the set threshold followed by the authors of that specific study. Five studies who implemented this sensitivity analysis approach failed to give justification regarding the ranges of variables used in their analysis.[21,22,29,37,39] On the other hand, in most studies that implemented a probabilistic sensitivity analysis, the probability of R-CHOP being a cost-effective treatment option over CHOP was high.[21-23,25,29,37,38] This, however, was not implemented by one study included in this review.[39]

Methodological Assessment

The systematic review utilized four critical appraisal tools to assess the quality of included studies: (1) the 2022 CHEERS checklist, (2) Cooper's Potential Hierarchies of Data Sources, (3) Drummond's Checklist, and (4) ECOBIAS, which are shown in Appendices G-J.

The CHEERS checklist revealed that studies reported on average 82.14% of required items, with 40% ranked as high quality and 60% as moderate quality. Cooper's Potential Hierarchies of Data Sources showed that most studies used high-ranked evidence for clinical effect sizes, baseline clinical data, resource use, and costs, while utilities were primarily derived from medium-ranked sources. Drummond's Economic Evaluation Checklist rated 30% of studies as good quality and 70% as moderate quality, with common deficiencies in reporting viewpoints, effectiveness study details, and sensiti-vity analysis justifications.

The ECOBIAS assessment identified potential biases in the studies, including narrow perspective bias, cost measurement omission bias, and limited time horizon bias. However, 90% of studies satisfied over 70% of the ECOBIAS criteria, with three studies achieving compliance with more than 80% of the defined criteria. Common areas for improvement across all appraisal tools included better reporting of study perspectives, more comprehensive cost considerations, and improved justification for methodological choices. Overall, while the studies demonstrated generally good methodological quality, there were areas where reporting and methodological rigor could be enhanced to improve the reliability and transparency of economic evaluations in this field.

DISCUSSION

The current study evaluated the cost-utility of R-CHOP against CHOP in the treatment of NHL in adult patients. The review included cost-utility analyses conducted in different countries between November 1997 and September 2023. The results of the systematic review suggested that the majority of the cost-utility analyses available at present were conducted in HICs and among these countries, R-CHOP is deemed more cost-effective than CHOP in the treatment of NHL in terms of utility measures. However, caution is advised when interpreting the results among countries of different income classifications.

This is the first systematic review within the past decade on the cost-utility of R-CHOP compared to CHOP in the treatment of NHL adult patients. This review included all cost-utility analyses conducted in different countries without limitation on language. It also made use of four validated methodological assessment tools for critically appraising and assessing the risk of bias of the included studies. There are limitations that may have affected the results of this systematic review. First, the authors did not perform a meta-analysis as initially planned due to insufficient data to provide a quantitative estimate of the cost-utility of R-CHOP against CHOP. A single estimate through meta-analytic procedures would have been useful in combining and synthesizing the results of the different cost-utility analyses. Second, the search string utilized could not be made more comprehensive because when other search terms such as specific NHL subtypes were employed, the search yielded specific results which were unable to satisfy the PICO. Because of this, the authors decided to use a more generalized search strategy instead. Third, the authors included a study which was written in Italian as the review did not exclude studies written in other languages besides English.[39] The study was translated by the authors with the use of Google Translate; however, the translation of the study was not verified by a professional translator. The reliability of the translation is therefore uncertain, which could affect the interpretation of the authors of this review.

Patient-specific Information

Intervention and Comparator

Variations in the intervention and comparator of the included studies were observed, specifically involving the dose and number of cycles of the treatment regimen in patients with DLBCL. The difference in the dose of one or more components of the treatment as well as the number of cycles is non-negligible as the costs for the treatment as a whole will also differ depending on them.

Oral Prednisone was given at a dose of 40 mg/m^2 (60%), 60 mg/m^2 (10%), and 100 mg/m^2 (20%). Various CPGs, such as NCCN, ESMO, NICE, and DOH CPG, did not specify the dose of Prednisone as well as the other components of CHOP.[10,27,44,45] Thus, the rationale behind the difference in dosing cannot be inferred. As all doses of Prednisone were considered high-dose, the decision on what dose to prescribe to patients lies with the prescribing physician or the principal investigator in the hospital and clinical trial setting, respectively.[18] It should be taken into consideration, however, that the study with Prednisone 60 mg/m^2 included DLBCL patients whose treatment status may be refractory, relapse, or remission compared to the studies with Prednisone 40 mg/m^2, which only included patients who were treatment-naive.[21-23,30] Furthermore, studies that reported using Prednisone 100 mg/m^2 primarily included FL patients in their evaluation.[25,26]

Additionally, two studies (20%) that included DLBCL patients and another two studies (20%) that included FL patients reported 6 cycles of CHOP and R-CHOP.[21,25,26,30] The other five studies (50%) reported 8 cycles of CHOP and R-CHOP.[22,29,30,37,39] Compared to the NCCN Guidelines on DLBCL, 4 to 6 cycles of R-CHOP for Stages I and II non-bulky and 6 cycles for Stages I and II bulky, III, and IV are recommended. However, the ESMO Guidelines suggest 8 cycles of R-CHOP for elderly patients. Considering that the mean age of the patients included in three studies is 60 years old while the mean age of the patients included in one study is 47 years old, it can be deduced that the age of the patient was potentially used to decide on the number of cycles used.[21,23,30,39]

Country-specific Information

Discount Rate and WTP

Most studies (60%) employed a 3% discount rate for costs and utilities, irrespective of the country's income level.[21,22,26,29,30,38] This is consistent with prevailing US guidelines recommending a 3% discount rate for economic evaluations in global health. While this rate is commonly recommended and aligned with HICs, it may not reflect the economic realities of LMICs, where a discount rate of 5 to 6% was generally more appropriate.[46] Additionally, the discount rates of 6% and 1.5% for costs and utilities, respectively by Berto et al. and Knight et al. aligned with the recommendations of the NICE guidelines for evaluating medical technologies within the framework of the English NHS.[23,39] On the other hand, the variations on rates of Groot et al., which applied a 4% discount rate for both costs and utilities, were in accordance with Dutch recommendations while Ray et al., which employed a 3.5% discount rate for both costs and utilities, claimed that their rate was based on NICE guidelines as well.[25,37]

As for the WTP threshold, only two studies (20%) adhere to the WHO-CHOICE recommendation, which set a threshold at three times the GDP per capita of the country as a criterion for determining the cost-effectiveness of health interventions.[29,30,47] Putri et al. chose a WTP threshold equal to the GDP of Indonesia, likely driven by the belief that utilizing the demand-side direct approach (WTP/QALY) could provide a more feasible method for determining a national threshold value within LMICs largely due to resource constraints and data limitations.[29,48] Among the three studies (30%) that established WTP thresholds tailored to their specific research, only Knight et al. conducted a threshold analysis on the main assumptions used to ensure that R-CHOP was not the preferred treatment strategy compared with CHOP for patients with DLBCL.[23] Ray et al. and Johnston et al., on the other hand, did not provide justification for the WTP threshold they employed.[25,38]

Study-specific Information

Study Perspective

In conducting economic evaluations, understanding the perspective from which an economic evaluation of a specific health intervention or technology was conducted is crucial as it establishes the parameters of the study and the kinds of costs and consequences or outcomes that are included in the analysis.[40] Different perspectives can significantly influence the findings of health economic studies as well as the recommendations and policies because they include or exclude different costs and outcomes. Therefore, when conducting, analyzing, or interpreting health economic assessments, it is imperative that the perspective be properly taken into account.

The included studies utilized various methodological perspectives. Berto et al. specified adopting a hospital perspective aligned with the framework of the National Health Service.[39] Best et al. conducted their analysis from the perspective of the French Social Security system, which finances public hospitals and reimburses specific medications, with patients typically bearing a nominal hospitalization fee, predominantly covered by a third-party payer (private insurance).[21] Ray et al. conducted their analysis from the perspective of the UK National Health Service.[25] Soini et al. asserted that they applied a healthcare provider perspective to their analysis, focusing solely on direct healthcare costs and excluding potential productivity losses, income transfers, and value-added tax.[26] Painschab et al. framed their costs and outcomes within a health systems perspective, encompassing overhead and capital costs.[30] Conversely, Knight et al., Groot

et al., Hornberger & Best, and Putri et al. explicitly mentioned employing a societal perspective or societal values aligned with their respective countries of origin.[22,23,29,37] However, Groot et al. specified that while their cost analysis was conducted from a societal perspective, it only encompassed direct medical costs.[37] Lastly, Johnston et al. failed to explicitly specify the study perspective they adopted.[38] Moreover, they neglected to provide explicit documentation of resource use, pivotal for determining the perspective employed in their analysis. This oversight can potentially introduce ambiguity regarding the framing of costs and outcomes within their analysis, thereby complicating accurate interpretation and assessment of their findings.

However, there are currently no strict international guidelines to classify study perspectives in economic evaluations. Consequently, it is challenging to consolidate the accurate perspective adopted by each included study. Discrepancies have also emerged between the perspectives reported in some studies and those outlined by Sittimart et al.[40] This prompted the authors to group the study perspectives into three broad categories: patient perspective, payer perspective, and societal perspective, drawing from the framework presented by Rascati.[49]

According to Rascati, the societal perspective encompasses various costs, including those incurred by the insurance company, patients, providers/institutions, and other sectors, and indirect costs stemming from productivity loss. Conversely, the predominant perspectives employed in pharmacoeconomic studies are typically either the institution/provider perspective (e.g., hospital or clinic) or the payer perspective (e.g., Medicaid or private insurance plan), as these are often more practical for addressing specific research questions. The payer perspective may involve expenses borne by the third-party plan, the patient, or a combination of patient co-payments and third-party plan costs. When analyzing from the hospital's perspective, it is essential to estimate the actual cost of treating a patient, analogous to determining the manufacturing cost of a product. Conversely, when analyzing from the payer's perspective, the reimbursement amount should be considered in cost estimation. Finally, when analyzing from the patient's perspective, expenses such as co-payments, deductibles, lost wages, and transportation costs should be estimated.[49]

Hence, the final categorization of the included studies is as follows: five studies embraced a healthcare payer perspective, four studies adopted a societal perspective, and the perspective utilized by Johnston et al. remains unclassified due to limited information available for definitive categorization.[21-23,25,26,29,30,37-39]

Model and Time Horizon

No specific guideline has been set in place regarding what time horizon is most applicable for use for pharmacoeconomic evaluations. NICE guidelines specified that time horizons used to estimate clinical effectiveness and value for money should adequately span long enough to reflect all of the important variations in costs and outcomes between health technologies being compared.[50] A cross-country comparison of health economic evaluations (HEE) guidelines showed that most national HEE guidelines advocate for the use of time horizons conceptually based on the natural course of the disease of interest along with the anticipated effects of the intervention.[51] The same review also noted that, at the minimum, the time horizon used should represent the duration of the randomized controlled trial evidence used to inform the analysis. For other studies, it is generally accepted that for chronic conditions such as cancer, lifetime horizons are more appropriately used since treatment for these diseases has high "up-front" costs with benefits being generated over a span of years rather than immediately.[52]

While the models used by the included studies have been tried and tested for use in economic evaluations, they may still cause errors which may affect the results of this review due to the inherent limitations of the models. Since data available for the population of interest is often not comprehensive enough, models and model parameters must still be curated data from already published literature or use estimates from calibrations with aggregate data.[53] Thus, assumptions that may lead to erroneous conclusions were still made during the analysis. Caution should still be taken when interpreting the results of this review.

Results of Economic Evaluations

Costs and Resource Use

The total costs for the CHOP regimen under a societal perspective ranged from $30,043.00 to $94,931.00 (in USD); €26,891.00 to €27,828.00 (in Euro); and £5,773.00 to £7,311.00 (in Pound), while the total costs for the R-CHOP regimen ranged from $42,777.00 to $105,847.00 (in USD); €40,171.00 to €42,751.00 (in Euro); and £14,456.00 to £15,181.00 (in Pound). On the other hand, the total costs for the CHOP regimen under a payer perspective were $1,776.00 (in USD); €4,589.00 to €49,562.00 (in Euro); and £20,922.00 (in Pound), while the total costs for the R-CHOP regimen were $5,100.00 (in USD); €19,427.00 to €59,521.00 (in Euro); and £29,794.00 (in Pound).

The costs of the treatment for NHL in the included studies were dependent on the study perspective adopted. Supposedly, more costs should be taken into account when a societal perspective is used compared to a payer perspective. However, in this review, only direct medical costs were measured by the majority of the included studies regardless of their chosen perspective. Of note, three out of four studies that adopted a societal perspective only reported direct medical costs.[22,23,37] As a result, the estimation of the total costs may have been lacking. In a cross-sectional analysis conducted by Griffiths et al., the inability to determine the actual costs incurred in the treatment of patients, including costs shouldered by health payers and patients, is more

evident in settings and diseases where the patients shoulder the majority of the costs.[47] It can be observed how there were varying trends on the costs reported between studies reported under a societal perspective and a payer perspective. Total costs in USD were higher in a societal perspective but total costs in Euro and Pound were higher in a payer perspective. It can be assumed that the studies with a societal perspective but were unable to account for all costs—direct and indirect—may have underestimated the costs incurred in the treatment of NHL patients.

Furthermore, as can be observed from the total costs of the regimens in the included studies, the total costs for R-CHOP were generally higher than CHOP which could be attributed to the addition of Rituximab in the treatment regimen. This is corroborated by the costing study conducted by Dzingirai et al., wherein the R-CHOP regimen had total costs of $2,950.00 per patient per cycle while the CHOP regimen only had $1,235.00. It was stated that 60% of the total costs for R-CHOP was attributable to medications while for CHOP, 52% was attributable to diagnostic procedures. This shows how the addition of Rituximab to CHOP significantly increases the costs related to medications in the treatment of NHL.[54]

Overall, it can be seen how costly the treatment for NHL can be, regardless of the treatment regimen. Specifically, chemotherapy costs (with or without Rituximab) mostly contributed to the total treatment costs. In a cross-sectional study conducted by Zakeri et al., they showed that patients with NHL have higher total health expenditures compared to any other cancers.[55] The health care expenditures included in the estimation of costs were hospitalization, outpatient care, emergency department, prescribed medications, dental care, vision, home health care, and other medical services, including ambulance, glasses, and other equipment. Among these, the major contributors to expenditures were hospital inpatient care, office-based visits, and prescription medications.[55] This is further supported by the study conducted by Mittman et al. which looked at the population-based healthcare costs related to NHL and compared it with non-NHL cohorts.[56] The study found that the costs for NHL were three to seven times higher than the non-NHL cohorts and the costs increased as the NHL stage increased. Among the costs accounted for, medications and inpatient care were found to be the major contributors.[56] This is similar to a retrospective cohort study conducted by Mounie et al. where cost-analysis showed that inpatient stay was principally the cost driver in the treatment of HL and NHL. Inpatient stay expenditures included hospitalization costs and cancer-related medications. The study also revealed that DLBCL was the most costly lymphoma subtype among HL and FL.[57]

Utilities

There are two main utility outcome measures being used in pharmacoeconomic evaluations—the first one looks at how effective health interventions are in improving life quality (QALYs), and the other focuses on the burden of disease in a population (DALYs).[58] The key difference between QALY and DALY lies on how they account for disability and illness. QALY focuses on the quality of life during the years lived, while DALY considers both the quality and quantity of life lost due to disability or illness. Like QALY, DALY expresses health outcomes in terms of years; however, DALY also incorporates disability weights, which reflect the severity of different health conditions on quality of life.

Standard measures of health outcomes include the EQ-5D, Health Utilities Index III (HUI III), SF36, Classification and Measurement System of Functional Health (CLAMES), QLQ-C30, MFI-20 instruments.[41,59] Using these, QALY can be described as perfect health being rated as 1 and being deceased as 0, with negative values indicating states worse than death. These values (referred to as weights or utilities) are assigned based on the preferences of the general public, often determined through tasks like time tradeoffs. On the other hand, the DALY scale has perfect health rated as 0 and death as 1, with no states currently recognized as worse than death. Disability weights are mainly determined through pairwise comparisons where individuals from the public decide which of two individuals is healthier. The primary goal is to measure health rather than preferences or utilities, although in practice, QALY and DALY weights are often similar. There is no currently a specific questionnaire prescribed for measuring either QALY or DALY, as both utility outcomes can originate from the same quality of life measure but are calculated differently, with DALY also considering disability weights.[60]

Additionally, there is a lack of consensus or clear recommendations regarding the preferred utility outcomes to be measured in economic assessments.[60] While global organizations like the WHO favor DALYs for comparing disease burdens between countries, QALYs are more commonly utilized in regions with established healthcare protocols. Nevertheless, there are no definitive criteria for determining the optimal outcome measure. This issue can be viewed as stemming from uncertainty surrounding the fundamental assumptions guiding researchers' decisions and their potential impact on results. Such uncertainty is just a facet of the broader uncertainty within healthcare, encompassing parameter variability and heterogeneity. Considering this, we cannot definitively assert the superiority or compare the prevalence of QALY usage in the majority of the included studies (90%) versus Painschab et al., who exclusively employed DALYs.[30]

Overall, the systematic review showed that R-CHOP was associated with higher QALY than CHOP alone in the study conducted in an LMIC and in the other studies countries in HICs; conversely, DALYs were found to be higher in patients receiving CHOP alone compared to R-CHOP in the study conducted in an LIC. These contradicting results highlight the need for guidelines describing which among QALY and DALY is preferred; this is both to standardize

outcomes reported and to allow for direct comparison or pooling of results in systematic reviews and meta-analyses. Further, it is important to note that the findings indicating higher DALYs in patients receiving CHOP alone as opposed to R-CHOP stems solely from the study conducted by Painschab et al. and it is therefore imperative to exercise additional caution when interpreting these results.[30]

As for the sources of utility measures, in three studies (30%), utility values were obtained through prospective methods.[29,30,39] Berto et al. conducted expert panel interviews, Putri et al. utilized patient interviews, and Painschab et al. relied on a clinical dataset from a prospective cohort.[29,30,39] The remaining studies (70%), on the other hand, employed retrospective methods.[21-23,25,26,37,38] They sourced utility values from various clinical trial studies and databases such as the GELA Trial, EORTC20981, Weeks et al., Van Agthoven et al., Doorduijin et al., and the Scottish and Newcastle Lymphoma Group (SNLG) database.[41,61-65]

In pharmacoeconomic evaluations, the choice between prospective and retrospective data depends on various factors, including research objectives, available resources, timeline, and data quality. Prospective data are preferred when detailed and accurate information on costs, outcomes, and resource utilization is essential, especially for evaluating new interventions or treatments. Retrospective data, on the other hand, can be valuable for assessing real-world effectiveness, healthcare utilization patterns, and long-term outcomes across larger populations. Combining both prospective and retrospective data may also provide a more comprehensive understanding of the economic impact and value of healthcare interventions. However, this requires careful consideration of potential sources of bias, heterogeneity, and data quality to ensure the validity and generalizability of the review findings across different scenarios.

Cost-Utility of R-CHOP

The majority of the included studies (90%) reported that R-CHOP was more cost-effective than CHOP in the treatment of NHL patients, as the ICURs reported from these studies were below the WTP thresholds of their corresponding countries.[21-23,25,26,29,37-39] It shall be noted, however, that a large portion of these studies were conducted in HICs, with WTP higher than other income groups. This is consistent with the current evidence on how economic evaluations are saturated in HICs.[66] The analysis showed that there are more than 1,200 economic evaluations published annually, of which 83% studied HICs, 14% studied UMICs, 4% studied LMICs, and 4% studied LICs. The sum exceeds 100%, as some economic evaluations studied multiple income groups. Regardless, most of the economic evaluations are concentrated in HICs, which corroborates the findings of this review. It is therefore imperative to determine the generalizability of the results to other income groups, specifically among LICs.

The remaining 10% of the studies reported an ICUR above their respective WTP threshold, indicating that CHOP is more cost-effective than R-CHOP. Painschab et al. revealed the factors that could have resulted in the deviation of their results from previous cost-utility analyses on R-CHOP in NHL patients.[30] Among the methodological differences stated by the study, the most relevant difference was that the authors have accounted for indirect costs, including costs for personnel and supplies, which all of the included studies failed to do so, even those that adopted a societal perspective.

Despite this, current evidence corroborates R-CHOP as the more cost-effective option. In a systematic review conducted in 2009 by Yoder and Kamal, R-CHOP was deemed more cost-effective than CHOP in terms of LYG and QALY.[67] They deduced that input data, assumptions, and sensitivity analyses have a significant impact in obtaining valid results and that policy- and clinical decision-makers should be able to account for the unique costs that are regarded as relevant to the country. In another systematic review conducted in 2012 by Auweiler et al. which assessed the cost-effectiveness of R-CHOP in the treatment of NHL through different types of economic evaluations, the ICURs per LYG and QALY from all of the included studies were below their respective WTPs.[31] Furthermore, R-CHOP was deemed as the cost-effective treatment in all sensitivity analysis scenarios. However, both of these reviews were published a decade ago, which raises questions about their applicability and relevance to the current situation in the treatment of NHL patients. Relevant stakeholders shall take cautionary measures when applying the results of these studies in their respective countries.

Sensitivity Analysis

Sensitivity analysis should be performed to address uncertainties involved in the sources of input parameters and the estimation of the input parameters used in the analysis. Since most CUAs also use surrogate endpoints to estimate QALYs, the uncertainties associated with the relationship between surrogate endpoints and final outcomes should also be quantified and presented. This should be shown through probabilistic sensitivity analysis and further explored in scenario analysis.[50] Out of the ten studies included in this review, nine (90%) studies carried out a probabilistic sensitivity analysis. In these studies, the probability of R-CHOP being a cost-effective treatment option over CHOP was high. One-way sensitivity analysis was also performed by nine (90%) out of the ten included studies. This analysis showed that, while ICURs were generally insensitive to changes made in the key assumptions used, time horizon was the factor that had the most significant impact on the ICURs. This may be because costs for treatment of chronic diseases such as cancer are higher in the first few months of treatment while benefits only accrue years after.[52] Because of this, ICUR values may fluctuate with longer or shorter time horizons. Thus, time horizons applied must be appropriately chosen for the disease of interest to give

a more accurate result to the analysis. Finally, five (50%) of the studies included were not able to justify the ranges of values they used for their sensitivity analysis.[21,22,29,37,39] The other five (50%) studies claimed to have based their ranges on published data and confidence intervals around the means of the stochastic data they used.[23,25,26,30,38] This may also be the case for the five aforementioned studies, however, this cannot be said for certain since they did not provide any justification nor did they disclose possible sources of the ranges they used for their sensitivity analysis.

Methodological Assessment Results

2022 CHEERS Checklist

In the CHEERS 2022 Statement, all ten (100%) of the studies failed to include the following in their economic analyses: (1) a health economic analysis plan, (2) characterization of heterogeneity, (3) characterization of distributional effects, (4) an approach to engagement with patients and others affected by the study in their methods, and the (5) effect of engagement with patients and others affected by the study.[21-23,25,26,29,30,37-39]

To date, there are still no standardized guidelines requiring the use of health economic analysis and while it is recommended for authors to, at least, indicate whether or not they developed a health economic analysis plan, it is not yet required. Further, this particular plan is more focused on economic evaluations which are being conducted alongside randomized controlled trials. It is still useful for all types of economic evaluations thus its future use should be considered.

The included studies also failed to characterize heterogeneity. It is recommended by Husereau et al. for heterogeneity to be separated from uncertainty when interpreting findings.[52] It is important for considerations to be made regarding how heterogeneity may arise so that it can be appropriately explored and its effects on the study's results can be appropriately reported. Because of this, authors are encouraged to describe the methods they used to investigate potential types of heterogeneity, and should they assume homogeneity among their population, justifications should also be given.

All of the studies also failed to report the distributional effects of the study.[21-23,25,26,29,30,37-39] This is very important especially when the results of the study are set to be used by decision-makers to determine the equity impacts of the interventions being evaluated in terms of social variables such as socioeconomic status, ethnicity, geographical location, or disease categories. Therefore, it is recommended for authors to describe any methods they may have used to address distributional concerns. The underpinning premise for characterizing these effects should also be mentioned. However, if these distributional concerns are not considered or included in the analysis, a statement declaring the fact should be present.

Another parameter that all the studies failed to report was the approach to engagement with patients and others who may be affected by the study.[21-23,25,26,29,30,37-39] Inclusion of relevant stakeholders, especially those directly affected by the decision made in these economic analyses, in all aspects of decision-making, implementation, and policy-making may help provide significant insights that can help optimize resource allocation across more diverse settings. Even though the act of engaging the community in pharmacoeconomic evaluations is still not established, involving stakeholders may help to improve transparency, accountability, and optimal resource allocations across a diverse setting. Reporting of the inclusion of community engagements to the studies will also help define what their specific contributions may be to research.

Finally, all ten studies also did not touch on the effect of engagement with patients and others who may be potentially affected by the study in their results.[21-23,25,26,29,30,37-39] One of the key areas of reporting includes the impact of involving relevant stakeholders in the research. When these groups are involved as active collaborators in the study, the authors are encouraged to report any difference this may have made in their study to show its effect.

Conversely, all ten (100%) studies were able to present their (1) selection of outcomes, (2) measurement of outcomes, (3) measurement and valuations of outcomes, summary of main results, and effect of uncertainty.[21-23,25,26,29,30,37-39] These parameters are all expected to be present since they are used for the analysis and interpretations done by the studies.

The CHEERS checklist is primarily intended to be used as a guide by researchers, reviewers, and editors in determining what should be reported and/or included in a comprehensive economic evaluation. This list enumerates the minimum amount or information required to be reported by a published health economic evaluation to help readers and reviewers in the interpretation and use of the studies. Since there are five items in the checklist that have not been included in all ten of the included studies, caution is advised when interpreting the results of this review since there may be vital unreported information that can affect the results of this study.

Cooper's Potential Hierarchies of Data Sources

In the majority of the studies (70%) with the use of Cooper's Potential Hierarchies of Data Sources, high-ranked evidence was used for four out of five components, specifically, clinical effect sizes, adverse events and complications, baseline clinical data, resource use, and costs.[21,23,25,26,29,30,39] The sources most used by the studies were RCTs, study-specific case series and analysis of administrative databases, previous prospective data collection, and cost calculations based on reliable databases and data sources.

Meanwhile, the sources for utilities in most studies (80%) were direct utility assessments from previous studies, which were ranked third in the hierarchy and considered

medium-ranked evidence.[21-23,25,26,37-39] It shall be noted that the only difference between the first and third-ranked sources is that the first-ranked sources, i.e., direct utility assessment for the specific study, consist of primary data while the third ranked sources, i.e., direct utility assessment from a previous study, consist of secondary data. The use of primary data collection allows the data to be contextualized based on the specific research question, leading to more reliable results.[68] Considering that utilities are self-reported data, they can vary widely from population to population. Thus, primary data offers a greater advantage as the actual quality of life of their population is gathered instead of the use of the quality of life from other populations which have their own distinct characteristics.

Cooper et al. warns the user of the hierarchy that the lack of higher ranking sources should not be a reason to stop conducting economic analyses, rather, it should only be viewed as a consensus statement that can guide end-users on which sources available is the best to use, regardless if it is in the lower levels of the hierarchy.[34]

Drummond's Economic Evaluation Checklist

The following information were mostly not stated or justified in the included studies: (1) viewpoints of the analysis, (2) details of the design and results of effectiveness study, (3) details of the methods of synthesis or meta-analysis of estimates, (4) details of the subjects from whom valuations were obtained, (5) separate reporting of quantities of resource use and unit costs, (6) the choice of variables for sensitivity analysis, and (7) the ranges over which the variables are varied.

A lack of clear perspective makes it difficult to grasp the contextual nuances and potential biases affecting result interpretation, potentially weakening the robustness and relevance of the study findings. Insufficient detail about study design and outcomes impedes the assessment of evidence quality and applicability, risking incomplete or inaccurate conclusions. Transparent reporting of synthesis methods is pivotal for gauging the validity and reliability of synthesized evidence; without it, the suitability of methods and the credibility of results are hard to ascertain. Similarly, understanding the characteristics of valuation subjects is crucial for assessing the generalizability and utility of economic evaluations, with missing details hindering the evaluation of valuation representativeness and relevance to the systematic review.

Furthermore, separating resource usage from unit costs is essential for clarity and transparency in economic evaluations; without this distinction, comprehending resource allocation and associated costs becomes challenging, potentially leading to confusion or misinterpretation. Sensitivity analysis, meanwhile, serves to test the robustness of economic evaluations by examining how varying key parameters impact results. However, without clear documentation of variable selection criteria and the extent of variation, it becomes unclear how sensitivity analyses were performed and whether the results are robust to uncertainties or variations.

Understanding the range of variation in sensitivity analysis is vital for interpreting findings and assessing the stability of economic evaluations. The absence of such information makes it difficult to gauge the potential impact of parameter uncertainties on study results. Ultimately, the lack of stated or justified information in the included studies may signify poor reporting practices, methodological shortcomings, or limitations in the original research. These deficiencies compromise the reliability, validity, and applicability of the evidence base, potentially undermining the integrity and usefulness of SR findings. The absence of this information may stem from various factors, including limitations in the scope of the included studies, methodological constraints, or reporting practices. Nonetheless, their exclusion could compromise the comprehensiveness, relevance, and interpretability of their findings, potentially limiting their usefulness for informing policy and practice.

Bias in Economic Evaluation (ECOBIAS)

Among the included studies, nine studies (90%) were able to comply with at least 70% of the criteria.[22,23,25,26,29,30,37-39] Notably, there were two criteria that all studies were not able to comply with—intermittent data collection bias and bias related to internal consistency.

Intermittent data collection bias is related to whether or not resource use was continuously collected. In the estimation of costs and utilities, especially when a societal perspective is adopted, the use of healthcare databases, insurance records, and other sources may not be sufficient to account for all the costs associated with their treatment as out-of-pocket expenses of the patients are not included in the estimation. Only the patient can truly provide the total scope of their healthcare utilization. As a result, underestimation of costs and resource use is highly possible. For instance, intermittent data collection is susceptible to missing important changes in one's treatment such as hospitalization or purchase of expensive medical devices. Despite this, the burden continuous data collection imposes on patients commonly results in missing values and participant withdrawal which is why, although it is the first choice, intermittent data collection is often performed instead. Therefore, instead of avoiding the use of intermittent data collection, the method by which it is performed should be appropriately planned. Random cohort data collection using three random cohorts is said to obtain the best estimation of total annual costs.[69]

The other criterion that was not met by all included studies is the internal consistency bias. Internal consistency bias occurs when no mathematical method, such as Cronbach's alpha, is performed to assess the interrelatedness of the variables within a study.[70] This is consistent with the results from the study conducted by Cooper et al. where out of the 42 included studies with economic models, only one study (2%) was able to mathematically assess and report internal consistency.[34] As economic evaluations make use of questionnaires to obtain the quality of life data of patients,

internal consistency is necessary to be measured using validated and appropriate mathematical methods.

On the other hand, a criterion on reporting and dissemination bias was deemed not applicable in all included studies considering that all of them were not conducted alongside a clinical trial, which is the only time where the study is required to be listed in a trial register. Reporting and dissemination bias occurs when authors fail to list their studies in registers or deviation from the study protocol without justification is observed. In reporting and dissemination of health economic evaluations, transparency and structure are essential for three reasons: (1) published economic evaluations are continuously rising; (2) significant opportunity costs depend on the decisions made based on the results of economic evaluations; and (3) no widely implemented mechanisms for warehousing data to allow for independent checking such as ethics review proceedings, regulator dossiers, or study registries. Thus, other methods to assess the quality of reporting and dissemination such as reporting guidelines (e.g., CHEERS) are used instead.[33]

Overall Recommendations on the Quality of Included Studies

The majority of the included studies compiled moderately with the required information outlined in the guidelines for economic evaluation set by the CHEERS checklist. However, all ten studies failed to include the following in their studies: (1) a health economic analysis plan, (2) characterization of heterogeneity, (3) characterization of distributional effects, (4) an approach to engagement with patients and others affected by the study in their methods, and the (5) effect of engagement with patients and others affected by the study. It is recommended for all economic evaluations to fully comply with the minimum information required by the CHEERS checklist to ensure the completeness of the data they present to help the readers and reviewers get a more comprehensive understanding of the study and thus aid them in interpreting its results and conclusions.

In terms of the compliance of the included studies to the hierarchies of data sources discussed by Cooper et al.,[34] the majority of the included studies used high-ranked evidence for most of the components except utilities. Most of the studies obtained their utility data from previous studies, which is considered as medium-ranked evidence. Thus, it is recommended that economic evaluation studies assess the quality of life of their patients through direct utility assessment specifically conducted for their study. The sample can be sourced from the general population, individuals with knowledge of the disease of interest, and patients with the disease of interest. If direct utility assessment is not possible, indirect utility assessment can be performed instead, provided that the sample includes patients with the disease of interest and the tool used to assess their quality of life is validated for the patient population.

The validity of the included studies was deemed to be only moderately valid according to Drummond's Checklist. This is primarily because crucial information such as the viewpoints of the analysis, design, and results of effectiveness studies, methods of synthesis, subjects' valuations, separate reporting of quantities of resource use and unit costs, variables for sensitivity analysis, and ranges of variable variation, were either not provided or justified poorly, scoring lower than 70% of the checklist. This oversight may undermine the reliability, validity, and applicability of the results potentially diminishing the integrity and utility of the systematic review findings. Various factors like scope limitations, methodological constraints, or reporting practices may have contributed to the absence of this information. Nevertheless, it is important to emphasize that the exclusion of these details could compromise the depth, relevance, and interpretability of the results, thereby limiting their value to policy and practice.

The included studies were generally not at a high risk of bias according to ECOBIAS, as the majority of the studies were able to comply with at least 70% of the risk of bias tool's criteria. However, all studies were not able to comply with bias related to intermittent data collection and internal consistency. To address bias related to intermittent data collection, it is recommended that economic evaluation studies perform continuous data collection as much as possible to avoid potential underestimation of costs involved in the treatment of NHL. If continuous data collection is not viable due to justifiable reasons such as dominant participant withdrawal, the data collection method to be used shall be appropriately selected and justified. Meanwhile, to address bias related to internal consistency, the economic evaluation studies are recommended to perform appropriate mathematical methods, such as Cronbach's alpha, to assess the interrelatedness of the variables included in their studies. Furthermore, there were criteria that the majority of the studies were not able to clearly report, such as biases related to sensitivity analysis, sponsors, and scope limitations. It is recommended that economic evaluation studies be more vigilant in reporting how they address the four principles of uncertainty—methodological, structural, heterogeneity, and parameter—and to make their study protocol freely available to the public.

With considerations to the above-mentioned results of methodological assessment tools, the results of this systematic review shall be interpreted with caution as there were criteria in each critical appraisal and risk of bias tools that the included studies were not able to comply with.

CONCLUSION AND RECOMMENDATIONS

The results of this review shall be interpreted with caution as the majority of the included studies favoring R-CHOP over CHOP for the treatment of NHL in terms of utility outcomes were concentrated in HICs. Hence, issues on the

generalizability of the results to other income classifications may arise as limited studies were included from LMICs and LICs, and no study was included from UMICs. The scarcity of published economic evaluations in these countries contributed to the limited or the lack of studies included in this review. More economic evaluations from LICs, LMICs, and UMICs are needed to arrive at a more robust and comprehensive conclusion regarding the cost-utility of R-CHOP over CHOP in the treatment of NHL.

This review also showed that there were several methodological differences present among the included studies, considering that each country has their own guidelines to follow when conducting economic evaluations. Methodological limitations were also observed from the results of the critical appraisal of the studies, particularly the completeness of the data reported, and the credibility of the sources used. Both of these observations highlight the importance of having an internationally recognized guideline to consolidate the methodological differences and limitations that could partly or wholly have an effect on the results of the economic evaluations. Of note, the guideline should focus on recommending the appropriate pharmaco-economic method, perspective, model, costs, outcomes, time horizons, and sensitivity analysis to be used given a particular research question.

It is recommended to conduct economic evaluations specific to the Philippines in order to develop context-specific information on the use of R-CHOP in the treatment of Filipino NHL patients. Moreover, it is recommended to conduct economic evaluations of varying designs besides CUA to capture a broader spectrum of cost-benefit outcomes. Once enough data has been generated, it is highly suggested to conduct a meta-analysis on the economic evidence of R-CHOP versus CHOP in order to pool available data and provide statistically significant recommendations that can help support health funding decision-making.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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APPENDICES

Appendix A. Identified Keywords for the Search Strategy

Component	Keyword
Population	Non-Hodgkin's Lymphoma Non-Hodgkin Lymphoma NHL Adult
Intervention/ Comparator	Rituximab Cyclophosphamide Hydroxydaunorubicin (Doxorubicin) Oncovin (Vincristine) Prednisone CHOP R-CHOP
Outcome	Quality of Life (QoL) Health-related Quality of Life (hrQoL) Disability-Adjusted Life Years (DALY) Quality-Adjusted Life Years (QALY) Incremental Cost-Utility Ratio (ICUR) Incremental Cost-Effectiveness Ratio (ICER) Incremental Net Benefit (INB)
Study Characteristics	Cost-utility analysis CUA

Appendix B. Screening Eligibility Form

Screening Eligibility Form					
Title of the Article:					
Database:					
Link to Article:					
Selection Criteria		**Yes**	**No**	**Unclear**	**Comments**
Inclusion Criteria					
Population of of Interest: Does the study include adult patients diagnosed with Non-Hodgkin's Lymphoma?		☐	☐	☐	
Intervention of Interest: Does the study population include patients treated with R-CHOP regimen?		☐	☐	☐	
Comparator of Interest: Does the study population include patients treated with CHOP regimen?		☐	☐	☐	
Reported Outcomes: Does the study measure the cost-effectiveness of CHOP and R-CHOP treatments in terms of health-related quality of life, quality-adjusted life years, disability-adjusted life years, Incremental Cost-Utility ratios and/or Incremental Net Benefits?		☐	☐	☐	
Study Design: Does the study employ a cost-utility design?		☐	☐	☐	
Type of Publication: Is the study an original article?		☐	☐	☐	
Date of Publication: Is this article published from November 1997 to September 2023?		☐	☐	☐	
Date of Publication: Was the study published from November 1997 to September 2023?		☐	☐	☐	
Exclusion Criteria					
Duplicates: Is the study a duplicate of another study already screened for eligibility?		☐	☐	☐	
DECISION (✓)	[ ] INCLUDE [ ] EXCLUDE				
Reason for Exclusion	[ ] Not relevant to Population [ ] Not relevant to Intervention [ ] Not relevant to Comparator [ ] Not relevant to Outcomes [ ] Not a cost-utility study [ ] Study is a duplicate				
Screened by:					
Date:					

Appendix C. Data Extraction Form

Data Extraction Form			
Data	**Present**	**Absent**	**Details**
General Information			
Article ID	☐	☐	
Title of Article	☐	☐	
Name of Authors	☐	☐	
Email of Corresponding Author	☐	☐	
Affiliation of First Author	☐	☐	
Journal Published	☐	☐	
Year of Publication	☐	☐	
Funding Source	☐	☐	
Conflict of Interest	☐	☐	
Study-Specific Characteristics			
Country Studied	☐	☐	
Type of Country Income	☐	☐	
Study Design (e.g., CUA with model-based, primary CUA alongside RCT/cohort)	☐	☐	
Study Perspective	☐	☐	
Discount Rate for Cost	☐	☐	
Discount Rate for Utility	☐	☐	
Currency, Currency-year	☐	☐	
Willingness to Pay (WTP) or Cost-effectiveness Threshold	☐	☐	
Time Horizon	☐	☐	
Type of Economic Model	☐	☐	
Health States/Nodes	☐	☐	
Participant Characteristics			
Type of Cancer	☐	☐	
Specific Type of NHL	☐	☐	
Stage (I, II, III, IV)	☐	☐	
Treatment Status (Naive, Recurrent, Refractory)	☐	☐	
Age (mean, SD)	☐	☐	
Sex (M, F) or Sex Ratio	☐	☐	
Source of Participants			
Costs and Resource Use	☐	☐	
Utilities	☐	☐	
Other Outcomes	☐	☐	
Sample Size			
Costs and Resource Use	☐	☐	

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Appendix C. Data Extraction Form *(continued)*

Utilities	☐	☐	
Other Outcomes	☐	☐	
Interventions and Comparators			
Treatment Intervention			
Dose	☐	☐	
Route	☐	☐	
Frequency	☐	☐	
Number of Cycles	☐	☐	
Treatment Comparator			
Dose	☐	☐	
Route	☐	☐	
Frequency	☐	☐	
Number of Cycles	☐	☐	
Other Treatment Comparators			
Components	☐	☐	
Dose	☐	☐	
Route	☐	☐	
Frequency	☐	☐	
Number of Cycles	☐	☐	
Outcome Measures			
Costs and Resource Use			
Type of Cost (e.g., direct cost, indirect cost)	☐	☐	
Direct Cost Incurred	☐	☐	
Variance of Direct Cost Incurred	☐	☐	
Indirect Cost Incurred	☐	☐	
Variance of Indirect Cost Incurred	☐	☐	
Total Cost Incurred	☐	☐	
Variance of Total Cost Incurred	☐	☐	
Utility Measures			
Tool Used to Measure Utility Outcomes	☐	☐	
Type of Utility Measures (e.g., hrQOL, QALY, DALY)	☐	☐	
hrQoL	☐	☐	
Variance of hrQOL	☐	☐	
QALY	☐	☐	
Variance of QALY	☐	☐	
DALY	☐	☐	
Variance of DALY	☐	☐	
Cost-Utility Outcomes			
ICUR	☐	☐	

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Appendix C. Data Extraction Form *(continued)*

Variance of ICUR	☐	☐	
INB	☐	☐	
Variance of INB	☐	☐	
Conclusion(s)	☐	☐	
Other Outcomes			
Type of Outcomes (Clinical, Economic, Humanistic)	☐	☐	
Reported Outcomes	☐	☐	
Sensitivity Analysis			
Type of Sensitivity Analysis	☐	☐	
Variables	☐	☐	
Results	☐	☐	

	Data Required	Data Availability	Data
1	Willingness to Pay (K)	☐	
2	Incremental Cost (ΔC)	☐	
3	Incremental Effectiveness (ΔE)	☐	
4	Incremental Cost-Effectiveness (ICER)	☐	
5	Variance of ΔC ($\sigma^2_{\Delta C}$)	☐	
6	Variance of ΔE ($\sigma^2_{\Delta E}$)	☐	
7	Covariance of ΔC and ΔE($\sigma_{\Delta E \Delta C}$)	☐	
8	Variance of ICER (σ^2_{ICER})	☐	
9	Confidence Interval (95%)	☐	
10	Upper limit of ICER (UL_{ICER})	☐	
11	Standardized normal ($Z_{a/2}$)	☐	
12	Mean ICER ($\hat{\upsilon}_{ICER}$)	☐	
13	Standard Error (SE)	☐	
14	Cost-effectiveness plane	☐	
15	Deterministic analysis means of cost, outcomes, and ICER	☐	

Legend:

- ☐ Scenario 1, if data from Rows 1 to 8 is present
- ☐ Scenario 2, if data from Rows 1-3, 9-12 is present, (optional: if row 13 is present)
- ☐ Scenario 3, if data from Rows 2, 3, 9, and 13 is present
- ☐ Scenario 4, if data from Row 14 is present
- ☐ Scenario 5, if data from Row 15 is present

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Appendix D. Search Strategy Used for each Database.

Database	Search Strategy
PubMED	(Non-Hodgkin Lymphoma) AND ((Rituximab AND Cyclophosphamide AND Doxorubicin AND Vincristine AND Prednisone) OR R-CHOP OR CHOP) AND ((cost-utility analysis OR cost-effectiveness analysis incremental cost-utility ratio OR incremental cost-effectiveness ratio OR incremental net benefit OR quality-adjusted life year OR disability-adjusted life year OR quality of life OR health-related quality of life") Publication Date: 1997-11-01 to 2023-09-30
SCOPUS	TITLE-ABS-KEY ((non-hodgkin* AND lymphoma OR nhl) AND ((rituximab AND cyclophosphamide AND (hydroxydaunorubicin OR doxorubicin) AND (oncovin OR vincristine) AND prednisone) OR r-chop OR chop) AND (("Cost-utility analysis" OR cua) OR ("Cost-effectiveness analysis" OR cea) OR ("incremental cost-utility ratio" OR icur) OR ("incremental cost-effectiveness ratio" OR icer) OR ("incremental net benefit" OR inb) OR ("quality-adjusted life year" OR qaly) OR ("disability-adjusted life year" OR daly) OR ("quality of life" OR qol) OR ("health-related quality of life" OR hrqol))) Publication Date: 1997-11-01 to 2023-09-30
Web of Science	ALL=(non-Hodgkin* lymphoma OR NHL) AND ((Rituximab AND Cyclophosphamide AND (Hydroxydaunorubicin OR Doxorubicin) AND (Oncovin OR Vincristine) AND Prednisone) OR R-CHOP OR CHOP) AND (("Cost-utility analysis" OR CUA) OR ("Cost-effectiveness analysis" OR CEA) OR ("incremental cost-utility ratio" OR ICUR) OR ("incremental cost-effectiveness ratio" OR ICER) OR ("incremental net benefit" OR INB) OR ("quality-adjusted life year" OR QALY) OR ("disability-adjusted life year" OR DALY) OR ("quality of life" OR QoL) OR ("health-related quality of life" OR hrQoL)) Publication Date: 1997-11-01 to 2023-09-30
EBSCOHost	(non-Hodgkin* lymphoma OR NHL) AND ((Rituximab AND Cyclophosphamide AND (Hydroxydaunorubicin OR Doxorubicin) AND (Oncovin OR Vincristine) AND Prednisone) OR R-CHOP OR CHOP) AND (("Cost-utility analysis" OR CUA) OR ("Cost-effectiveness analysis" OR CEA) OR ("incremental cost-utility ratio" OR ICUR) OR ("incremental cost-effectiveness ratio" OR ICER) OR ("incremental net benefit" OR INB) OR ("quality-adjusted life year" OR QALY) OR ("disability-adjusted life year" OR DALY) OR ("quality of life" OR QoL) OR ("health-related quality of life" OR hrQoL)) Publication Date: 1997-11-01 to 2023-09-30
Cochrane Library	(non-Hodgkin* lymphoma OR NHL) AND ((Rituximab AND Cyclophosphamide AND (Hydroxydaunorubicin OR Doxorubicin) AND (Oncovin OR Vincristine) AND Prednisone) OR R-CHOP OR CHOP) AND (("Cost-utility analysis" OR CUA) OR ("Cost-effectiveness analysis" OR CEA) OR ("incremental cost-utility ratio" OR ICUR) OR ("incremental cost-effectiveness ratio" OR ICER) OR ("incremental net benefit" OR INB) OR ("quality-adjusted life year" OR QALY) OR ("disability-adjusted life year" OR DALY) OR ("quality of life" OR QoL) OR ("health-related quality of life" OR hrQoL)) Publication Date: 1997-11-01 to 2023-09-30
York Research Database	(non-Hodgkin* lymphoma OR NHL) AND ((Rituximab AND Cyclophosphamide AND (Hydroxydaunorubicin OR Doxorubicin) AND (Oncovin OR Vincristine) AND Prednisone) OR R-CHOP OR CHOP) Publication Date: 1997-11-01 to 2023-09-30
The University of York Centre for Reviews and Dissemination Database	(Non-Hodgkin Lymphoma) AND ((Rituximab AND Cyclophosphamide AND Doxorubicin AND Vincristine AND Prednisone) OR (RCHOP OR R-CHOP) OR CHOP) AND ((Cost-Benefit Analysis OR (incremental cost-utility ratio OR ICUR) OR (incremental cost-effectiveness ratio OR ICER) OR (incremental net benefit OR INB) OR (quality-adjusted life year OR (disability-adjusted life year OR DALY) OR quality of life) Publication Date: 1997-11-01 to 2023-09-30
HERDIN	(non-Hodgkin* lymphoma OR NHL) AND ((Rituximab AND Cyclophosphamide AND (Hydroxydaunorubicin OR Doxorubicin) AND (Oncovin OR Vincristine) AND Prednisone) OR R-CHOP OR CHOP) AND (("Cost-utility analysis" OR CUA) OR ("Cost-effectiveness analysis" OR CEA) OR ("incremental cost-utility ratio" OR ICUR) OR ("incremental cost-effectiveness ratio" OR ICER) OR ("incremental net benefit" OR INB) OR ("quality-adjusted life year" OR QALY) OR ("disability-adjusted life year" OR DALY) OR ("quality of life" OR QoL) OR ("health-related quality of life" OR hrQoL)) Publication Date: 1997-11-01 to 2023-09-30

Appendixe E. General Characteristics of Included Studies

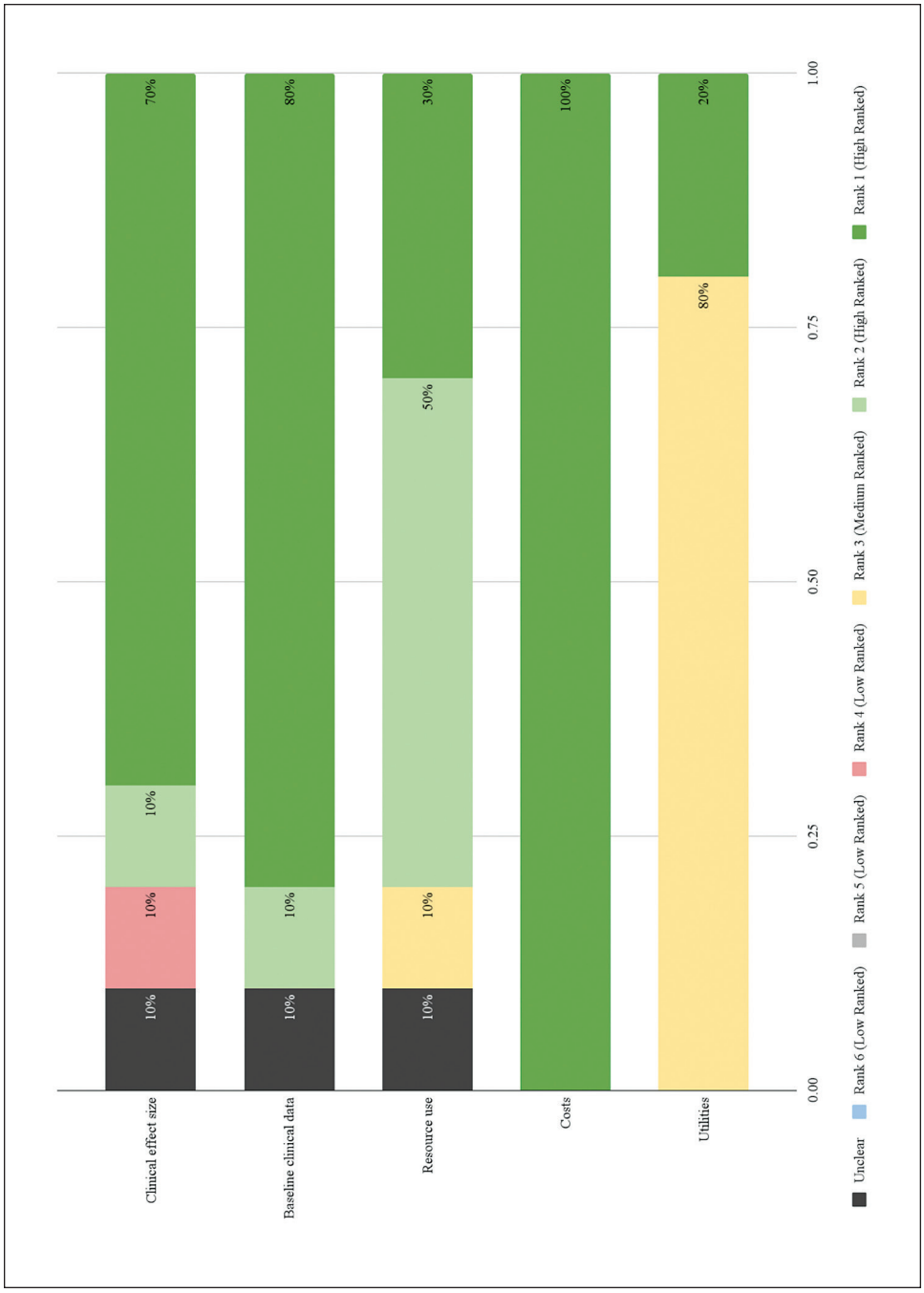
Study	Article ID	Affiliation of First Author	Journal Published	Publication Year	Funding Source	Conflict of Interest	Population
Berto et al., 2004	10.1007/BF03320633	PBE Consulting, Verona	International - PharmacoEconomics	2004	Roche Italia	Not reported	DLBCL
Knight et al., 2004	10.3310/hta8370	School of Health and Related Research (ScHARR), University of Sheffield, UK	International - Health Technology Assessment 2004	2004	HTA Programme on behalf of NICE as project number 02/17/01	Reported	DLBCL
Best et al., 2005	10.1111/j.1524-4733.2005.00037.x	Department of Pharmacy, University of Washington, Seattle,WA, USA	International - Value in Health	2005	F. Hoffmann-La Roche, Ltd.	Not reported	DLBCL
Groot et al., 2005	10.1111/j.1600-0609.2004.00368.x	Erasmus Medical Centre, Institute for Medical Technology Assessment	International - European Journal of Haematology	2005	Not reported	Not reported	DLBCL
Hornberger & Best, 2005	10.1002/cncr.20956	[1] Department of Clinical Economics, Acumen LLC/ The SPHERE Institute, Burlingame, California [2] Department of Medicine, Department of Veteran Affairs, Palo Alto, California [3] Department of Medicine, Stanford University, Stanford, California	International - American Cancer Society Journals	2005	Genentech, Inc.	Not reported	DLBCL
Johnston et al., 2010	10.1111/j.1524-4733.2010.00737.x	[1] Canadian Centre for Applied Research in Cancer Control (ARCC), British Columbia Cancer Agency,Vancouver, BC, Canada [2] School of Population and Public Health, University of British Columbia,Vancouver, BC, Canada	International - Value in Health	2010	[1] Terry Fox Foundation [2] Genome Canada/ Genome BC [3] Turner Family Lymphoma Outcomes donation to the British Columbia Cancer Foundation	Not reported	DLBCL
Ray et al., 2010	10.1111/j.1524-4733.2009.00676.x	F. Hoffmann-La Roche, Ltd., Basel, Switzerland	International - Value in Health	2010	F. Hoffmann-La Roche, Ltd.	Not reported	FL
Soini et al., 2011	10.1093/annonc/mdq582	ESiOR Oy, Kuopio, Finland	International - Annals of Oncology	2011	Roche Oy, Finland	Reported	FL
Painschab et al., 2021	10.1016/S2214-109X(21)00261-8	Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA; Division of Hematology, Department of Medicine, University of North Carolina, Chapel Hill, NC, USA; University of North Carolina Project Malawi, Lilongwe, Malawi	International - The Lancet Global Health	2021	National Institutes of Health	Reported	DLBCL
Putri et al., 2022	10.1186/s12913-022-07956-w	Health Policy and Administration Department, Faculty of Public Health & Center for Health Economics and Policy Studies (CHEPS) University of Indonesia, Depok, West Java, 16424, Indonesia.	BMC Health Services Research	2022	Indonesian Health Security Agency (BPJS Kesehatan)	Reported	DLBCL

Appendix F. Summary of the Country- and Study-specific Characteristics of Included Studies

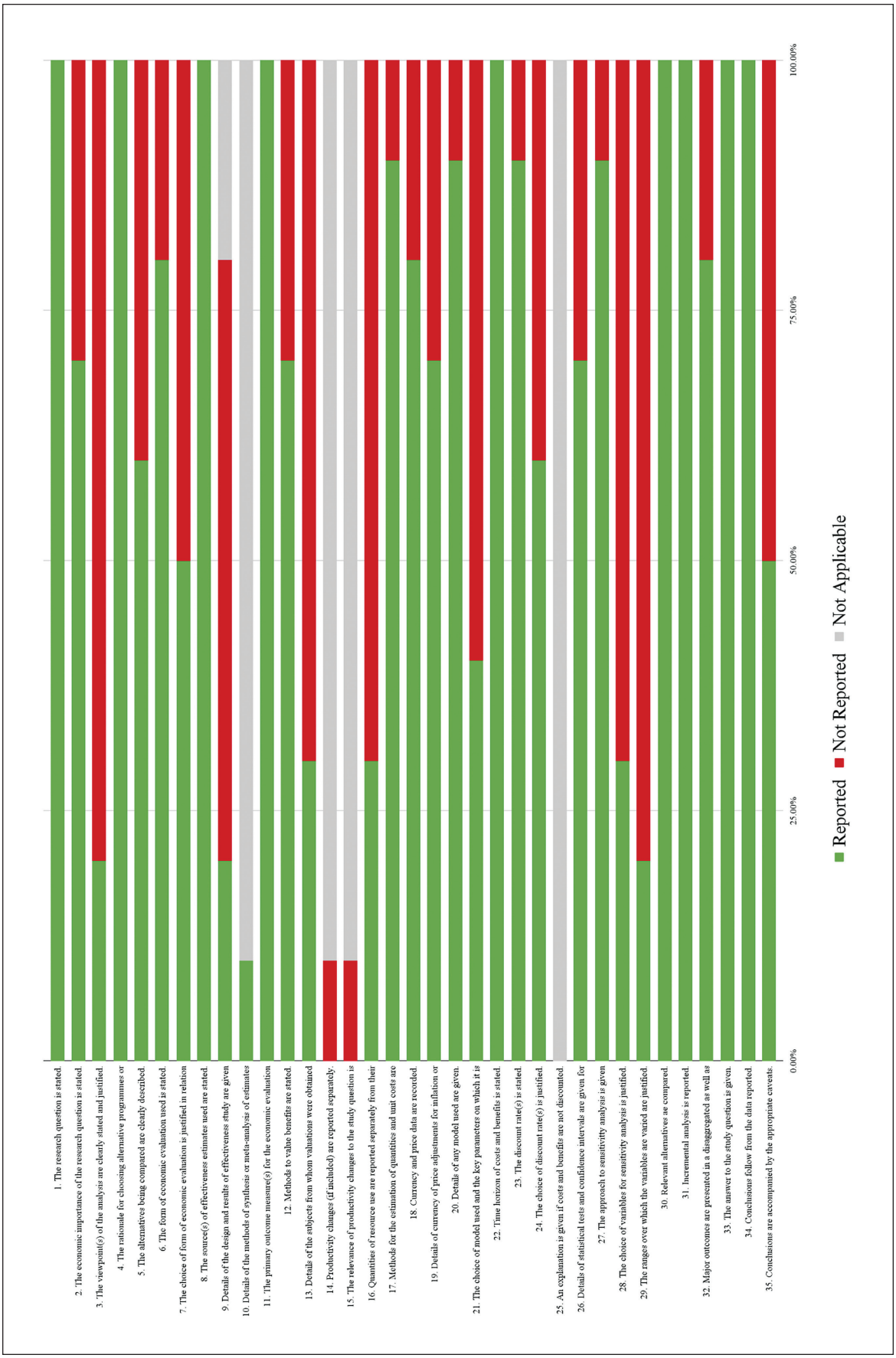
Study	Country	Study Design	Study Perspective	Type of Country Income	Discount Rate		Currency, year	WTP	ICUR (Discounted)	Time Horizon	Economic Model
					Cost	Utilities					
Europe											
Berto et al., 2004	Italy	CUA & BIA	Payer	HIC	6%	1.5%	Euro (€), N/A	Not stated	<60y/o: €13,362.00/QALY ≥60y/o: €12,879.00/QALY	15 years	Markov state-transition model, 5 health states
Knight et al., 2004	UK	CUA & SR	Societal	HIC	6%	1.5%	Pound (£), N/A	£30,000.00/ QALY	<60 y/o: £7,533.00/QALY ≥60 y/o: £10,596.00/QALY	15 years	Markov state-transition model, 3 health states
Best et al., 2005	France	CUA	Payer	HIC	3%	3%	Euro (€), 2003	Not stated	€12,259/QALY	15 years	Not stated
Groot et al., 2005	Netherlands	CUA	Societal	HIC	4%	4%	Euro (€), 2003	Not stated	<60 y/o: €13,983.00/QALY ≥60 y/o: €17,933.00/QALY	15 years	Markov State-transition model, 6 health states
Ray et al., 2010	UK	CUA	Payer	HIC	3.5%	3.5%	Pound (£), 2008	£20,000.00/ QALY	£10,676.00/QALY	Lifetime	Markov state-transition model, 3 health states
Soini et al., 2011	Finland	CUA	Payer	HIC	3%	3%	Euro (€), 2008	Not stated	€12,123.00/QALY	Lifetime	Markov state-transition model, 3 health states
America											
Hornberger & Best, 2005	USA	CUA	Societal	HIC	3%	3%	USD ($), 2003	Not stated	$19,297.00/QALY	5 years	Markov state-transition model, 5 health states
Johnston et al., 2010	Canada	CUA	Not stated	HIC	3%	3%	CAD (C$), 2006	C$50,000.00/ QALY	<60 y/o: C$19,411.00/QALY ≥60 y/o: C$5,853.00/QALY	15 years	Micro-simulation Model, 8 health states
Africa											
Painschab et al., 2021	Malawi	CUA	Payer	LIC	3%	3%	USD ($), 2017	$1,014.00/ DALY (3x 2017 GDP) $338.00/DALY (2017 GDP)	$1,204.00/DALY	Lifetime	Three-strategy decision-tree model
South-East Asia											
Putri et al., 2022	Indonesia	CUA	Societal	LMIC	3%	3%	USD ($), 2019	$11,538.00/ QALY (3x GDP)	$9,280.00/QALY	Lifetime	Markov state-transition model, 3 health states

Appendix G. Summary of 2022 CHEERS Checklist of Included Studies

Appendix H. Summary of Cooper's Potential Hierarchies of Data Sources of Included Studies



Appendix I. Summary of Drummonds Checklist of Included Studies



Appendix J. Summary of Bias in Economic Evaluation (ECOBIAS) Checklist of Included Studies

Authors	Berto et al., 2004	Knight et al., 2004	Best et al., 2005	Groot et al., 2005	Hornberger & Best, 2005	Johnston et al., 2010	Ray et al., 2010	Soini et al., 2011	Painschab et al., 2021	Putri et al., 2022
PART A. Overall checklist for bias in economic evaluation										
Narrow Perspective Bias	-	+	-	+	+	/	-	-	-	+
Inefficient comparator bias	+	+	+	+	+	+	+	+	+	+
Cost measurement omission bias	-	-	+	-	-	-	-	+	-	+
Intermittent data collection bias	-	-	-	-	-	-	-	-	-	-
Invalid valuation bias	+	+	-	+	?	+	?	+	+	+
Ordinal ICER bias	+	+	+	+	+	+	+	+	+	+
Double-counting bias	+	+	+	+	+	?	+	+	+	+
Limited sensitivity analysis bias	?	?	?	?	?	?	?	?	?	?
Sponsor bias	?	?	?	-	?	?	?	?	?	?
Reporting and dissemination bias	/	/	/	/	/	/	/	/	/	/
PART B. Model-specific aspects of bias in economic evaluation										
I. Bias related structure										
Structural assumption bias	+	+	-	+	+	+	+	+	?	+
No treatment comparator bias	+	+	+	+	+	+	+	+	+	+
Wrong model bias	+	+	-	+	+	+	+	+	+	+
Limited time horizon bias	+	?	-	-	+	-	-	+	+	+
II. Bias related to data										
Bias related to data identification	?	?	?	?	?	?	?	?	+	+
Bias related to baseline data	?	+	?	?	?	?	?	-	+	+
Bias related to treatment effects	+	+	+	+	+	+	+	+	+	+
Bias related to quality-of-life weights (utilities)	+	+	+	+	+	+	+	+	?	+
Non-transparent data incorporation bias	+	+	+	+	+	+	?	?	+	+
Limited scope bias	?	?	-	?	?	?	?	?	?	?
III. Bias related to consistency										
Bias related to internal consistency	-	-	-	-	-	-	-	-	-	-

Legends:
+ YES - NO ? PARTLY / UNCLEAR / NOT APPROPRIATE