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ABSTRACT

Objective Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone, once every 3 weeks (R-CHOP21) is commonly used in non-Hodgkin’s lymphoma (NHL), but accompanied by *Pneumocystis carinii* pneumonia (PCP) as a fatal treatment complication. This study aims to estimate the specific effectiveness and cost-effectiveness of PCP prophylaxis in NHL undergoing R-CHOP21.

Design A two-part decision analytical model was developed. Prevention effects were determined by systematic review of PubMed, Embase, Cochrane Library and Web of Science from inception to December 2022. Studies reporting results of PCP prophylaxis were included. Enrolled studies were quality assessed with Newcastle-Ottawa Scale. Costs were derived from the Chinese official websites, and clinical outcomes and utilities were obtained from published literature. Uncertainty was evaluated through deterministic and probabilistic sensitivity analyses (DSA and PSA). Willingness-to-pay (WTP) threshold was set as US$31,315.23/quality-adjusted life year (QALY) (threefold the 2021 per capita Chinese gross domestic product).

Setting Chinese healthcare system perspective.

Participants NHL receiving R-CHOP21.

Interventions PCP prophylaxis versus no prophylaxis.

Main outcome measures Prevention effects were pooled as relative risk (RR) with 95% CI. QALYs and incremental cost-effectiveness ratio (ICER) were calculated.

Results A total of four retrospective cohort studies with 1796 participants were included. PCP risk was inversely associated with prophylaxis in NHL receiving R-CHOP21 (RR 0.17; 95% CI 0.04 to 0.67; p=0.01). Compared with no prophylaxis, PCP prophylaxis would incur an additional cost of US$527.61, and 0.57 QALYs gained, which yielded an ICER of US$929.25/QALY. DSA indicated the WTP threshold was 0.17 and long-term outcomes of PCP prevention in the target populations.

Conclusion Prophylaxis for PCP in NHL receiving R-CHOP21 is highly effective from retrospective studies, and routine chemoprophylaxis against PCP is overwhelmingly cost-effective from Chinese healthcare system perspective. Large sample size and prospective controlled studies are warranted.

INTRODUCTION

Non-Hodgkin’s lymphoma (NHL) is a frequent haematological malignancy with significant morbidity and mortality.1 China recorded an estimated 92,834 new cases and 54,351 deaths of NHL that occurred in 2020, accounting for 17.05% incidence and 20.92% mortality of NHL in the world, respectively.2 Among NHL subtypes, more than one-third of all cases are diffuse large B-cell lymphoma (DLBCL), which is the most common subtype.3 Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is the first-line therapeutic regimen for DLBCL,

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A meta-analysis was conducted to generate accurate prevention effect of *Pneumocystis carinii* pneumonia (PCP) prophylaxis for patients with non-Hodgkin’s lymphoma receiving rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone, once every 3 weeks chemotherapy.

⇒ Cost-effectiveness analysis combining decision tree and Markov model was developed, which captured the short-term and long-term outcomes of PCP prevention in the target populations.

⇒ Only direct medical costs including drug costs, management costs for prophylaxis-associated adverse events, PCP treatment and chemotherapy costs were considered.

⇒ The Chinese healthcare system perspective may limit the extrapolation of the findings to other country settings.
which has been proved to have remarkable efficacy, with prominent 3-year progression-free survival (66.10%) and 3-year overall survival (77.60%). However, medical therapy is frequently accompanied by adverse reactions, some of which are fatal. Substantial evidence suggested that rituximab-containing regimens (especially R-CHOP chemotherapy) are one of the high-risk factors for *Pneumocystis carinii* pneumonia (PCP). The mortality of PCP is high, ranging from approximately 14% to 80% in haematological malignancies. Moreover, planned chemotherapy cycles may be terminated or delayed due to PCP, leading to poor anti-cancer effects.

Although life-threatening, the occurrence of PCP can be prevented by first-line regimens like trimethoprim/sulfamethoxazole (TMP/SMZ). Several studies have demonstrated that the occurrence of PCP in immunocompromised patients can be significantly attenuated by 73%–91% after prevention. Also, a meta-analysis published in 2015 supported the TMP/SMZ prevention efficacy with 72% reduction in the incidence of PCP in patients with lymphoma treated with rituximab-containing chemotherapy. However, there is a paucity of analysis of PCP prevention for the population confined to R-CHOP chemotherapy. With a growing body of evidence on PCP prevention emerges subsequently, updating the meta-analysis might obtain a more accurate efficacy data.

In addition, there are different recommendations about PCP prophylaxis for R-CHOP14 (on a 14-day interval) and R-CHOP21 (on a 21-day interval). For high-intensity chemotherapy regimen like R-CHOP14 with higher risk for PCP, prevention is recommended both in European and Australian guidelines. Although there is no established recommendation, recent evidence demonstrated that R-CHOP21 have a certain risk for inducing PCP and conflicting views persist regarding routine prophylaxis for PCP in this population. The specific efficacy data for PCP prevention in R-CHOP21 is absent on account of the fact that previous studies focused on a comprehensive population using all rituximab-based chemotherapy, including R-CHOP14 and fludarabine, cyclophosphamide and rituximab beyond R-CHOP21. Therefore, it is worth studying the effectiveness of PCP prophylaxis in patients receiving R-CHOP21, as well as the cost-effectiveness.

In this study, a meta-analysis was used to obtain the updated relative risk (RR) of PCP with prophylaxis versus no prophylaxis in R-CHOP21-treated NHL, and subsequently, the RR was employed in a two-part decision analytic model to evaluate the cost-effectiveness of PCP prophylaxis strategy during R-CHOP21 chemotherapy from the Chinese healthcare system perspective. The results might provide insight into the pros and cons of PCP prophylaxis strategy, and produce proof as reference for decision makers.

**METHODS**

**Patient and public involvement**

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

**Meta-analysis**

**Literature search**

Following the recommendations of the Cochrane Handbook and other published meta-analyses, databases including PubMed, Embase, Web of Science and the Cochrane Library were queried for relevant studies published from inception to December 2022. The original protocol for this meta-analysis was available in online supplemental appendix A. The search strategy adopted the combination of subject words with free words and key search terms included “lymphoma”, “rituximab” and “pneumocystis carinii pneumonia”. No filter was applied with the aim of picking up all potentially relevant data. To ensure a comprehensive search, we screened for grey literature by reviewing the bibliographies of included articles and previous meta-analyses. The full search strategies can be found in online supplemental appendix B.

**Study selection and data extraction**

Inclusion/Exclusion criteria were determined according to the PICOS framework:

- **(P)opulation**: patients with NHL undergoing R-CHOP21 chemotherapy.
- **(I)nterventions**: PCP primary prophylaxis was administered during R-CHOP21 treatment.
- **(C)omparisons**: PCP primary prophylaxis was not administered during R-CHOP21 treatment.
- **(O)utcomes**: documented PCP incidences.
- **(S)Types of studies**: original articles, including prospective and retrospective cohort studies and randomised clinical trials (RCTs); reviews, case reports, meta-analyses, editorials, letters and comments were excluded.

Selection of articles was conducted by two reviewers following the inclusion and exclusion criteria. The titles and abstracts were evaluated at first, then potentially relevant articles were obtained in full text and read for the final selection. The study information was independently extracted by two investigators, using predefined extraction forms; any conflict was resolved by a third reviewer.

**Study quality assessment**

Two researchers independently conducted quality assessment of included studies. Since all included studies were cohort study, the Newcastle-Ottawa Scale (NOS) was used. This instrument is usually used to assess the quality of cohort studies against three aspects: selection (four items, with each being awarded one star), comparability (one item, which can be awarded up to two stars) and outcome (three items, with each being awarded one star). A score of ≥7 stars is indicative of a high-quality study.

**Statistical analysis**

RevMan, V.5.4.1 was employed to perform all statistical calculations in this meta-analysis. Data were combined and estimated for a pooled RR, and 95% CI were calculated. If $I^2 \geq 50$ and $I^2 < 50$ were defined as high and low heterogeneity, respectively, and correspondingly random-effect
models or fixed-effect models were used. Funnel plot was used to evaluate publication bias.

Cost-effectiveness analysis

Model structure

The model of this cost-effectiveness analysis was developed with reference to cost-effectiveness analyses on the prevention for common complications of R-CHOP21, including hepatitis B virus reactivation and febrile neutropenia. A two-part decision analytic model was adopted and constructed by using TreeAge, V.2020 (figure 1). The cost-effectiveness of PCP prophylaxis in NHL receiving six cycles of R-CHOP21 as first-line treatment was evaluated in this study. The first part was a decision tree that simulated PCP prophylaxis concurrent with chemotherapy (figure 1A). The decision tree showed two different strategies applied to modelled cohorts. In prophylaxis strategy, patients would receive TMP/SMZ as primary prophylaxis for PCP during R-CHOP21 chemotherapy. Patients experiencing adverse events (AEs) due to PCP prophylaxis were considered in the model. The AEs that need treatment and would lead to discontinuation of the prophylactic drug were included, which were incorporated in the branch of receiving TMP/SMZ prophylaxis. Referring to PCP prophylaxis guidelines, this group of patients would switch to second-line prophylactic drugs, as shown in the branch of receiving pentamidine for prophylaxis. The duration of PCP prophylaxis was six cycles of R-CHOP21 treatment. In the other strategy, the prevention for PCP was not applied. Patients in two strategies have different probabilities to experience PCP, which would be classified into severe or non-severe infections based on the PaO2 while breathing room air or on the alveolar-arterial oxygen difference (AaDO2), prior to the first bronchoscopy. Specifically, the criteria for severe PCP were PaO2<60 mmHg or AaDO2≥45 mmHg. Patients could die or recover from PCP in corresponding probabilities. After R-CHOP treatment ending, the living patients would enter the Markov state-transition model for tracking long-term clinical and economic outcomes (figure 1B). Based on the relative dose intensity (RDI) of chemotherapy received, patients were stratified into two states, including standard (>90%) and reduced

Figure 1  Simplified schematic of (A) decision tree and (B) Markov state-transition frameworks. DLBCL, diffuse large B-cell lymphoma; M, Markov; NS-PCP, non-severe Pneumocystis carinii pneumonia; PM, pentamidine; RDI, relative dose intensity; S-PCP, severe Pneumocystis carinii pneumonia; TMP/SMZ, trimethoprim/sulfamethoxazole.
(≤90%) RDI. Given the increased proportion of ventilatory support and extended duration of treatment in severe PCP infections, patients experiencing a severe PCP would undergo a chemotherapy with reduced RDI, while the others would not. In addition, a ‘cure’ state was set in the Markov model since R-CHOP therapy has been shown in clinical trials to cure up to 60% of newly diagnosed cases. Patients who survived >5 years after first-line chemotherapy would enter ‘cure’ state in this model as survival of 5 years is usually considered as the time threshold for clinical cure. The state-transition model tracked patient time in yearly cycles across predefined health states.

Model inputs
Model inputs including clinical probabilities, costs and utilities were estimated based on data published in peer-reviewed journals or publicly available sources, which are listed in table 1 and table 2.

Probabilities
The prophylaxis effectiveness of TMP/SMZ were from our meta-analysis of 1796 patients with NHL receiving R-CHOP21 chemotherapy. The incidences of TMP/SMZ-related AEs resulting in discontinuation were obtained from a retrospective study, including liver dysfunction, kidney dysfunction, neutropenia, thrombocytopenia, anaemia, rash and electrolyte disturbance. Mortality of severe PCP (59.0%) and non-severe PCP (6.2%) were sourced from Monnet et al and Safrin et al, respectively. The overall survival curve from a phase III trial including 702 Chinese patients with DLBCL was used to estimate the cancer-specific postchemotherapy mortality for years 1–5. The mortality of patients cured after chemotherapy was assumed to be the age-specific mortality rates from Global Health Observatory data of China (http://apps.who.int/gho/data). RDI thresholds of 90% was based on published clinical data indicating that it was clinically meaningful RDI reduction in patients receiving R-CHOP21 therapy. The mortality hazard ratio (HR) for RDI ≤90% vs >90% was based on a study of patients with DLBCL, for which there was an HR of 0.30 for an average RDI of >90% vs ≤90%; the reciprocal HR of 3.33 was used in the model.

Cost estimations
Direct medical costs were included in present study, which contained drug costs, management costs for prophylaxis-associated AEs, PCP treatment and chemotherapy costs. For drug costs, the median price of the national drug winning bid in 2021 was searched in Yaozhi network (https://yaozh.com/). Oral TMP/SMZ 80 mg/400 mg daily was administered during R-CHOP21 chemotherapy.

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### Table 1 Probability parameters used in the model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Base-case value</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Distribution</th>
<th>Source</th>
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<tbody>
<tr>
<td><strong>Incidence of PCP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Without prophylaxis (%)</td>
<td>3.56</td>
<td>2.00</td>
<td>5.48</td>
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<td>MA</td>
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<tr>
<td>RR of PCP with TMP/SMZ</td>
<td>0.17</td>
<td>0.04</td>
<td>0.67</td>
<td>Log-normal</td>
<td>MA</td>
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<td>RR of PCP with PM</td>
<td>0.35</td>
<td>0.20</td>
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<td>Proportion of severe PCP (%)</td>
<td>78.60</td>
<td>62.88</td>
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<tr>
<td><strong>Incidence of AEs resulting discontinuation</strong></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Liver dysfunction (%)</td>
<td>5.33</td>
<td>4.26</td>
<td>6.40</td>
<td>Beta</td>
<td>22</td>
</tr>
<tr>
<td>Kidney dysfunction (%)</td>
<td>5.33</td>
<td>4.26</td>
<td>6.40</td>
<td>Beta</td>
<td>22</td>
</tr>
<tr>
<td>Neutropenia (%)</td>
<td>1.23</td>
<td>0.98</td>
<td>1.48</td>
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<td>Thrombocytopenia (%)</td>
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<td>1.64</td>
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<td>Electrolyte disturbance (%)</td>
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<td>Mortality of non-severe PCP (%)</td>
<td>6.20</td>
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<td>Mortality of severe PCP (%)</td>
<td>59.00</td>
<td>47.20</td>
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<td>Mortality HR for RDI ≤90% vs &gt;90%</td>
<td>3.33</td>
<td>2.17</td>
<td>5.00</td>
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<td><strong>Other relevant clinical data</strong></td>
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<tr>
<td>Risk of intolerance to TMP/SMZ (%)</td>
<td>17.62</td>
<td>14.10</td>
<td>21.14</td>
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<tr>
<td>Body surface area (m²)</td>
<td>1.65</td>
<td>1.28</td>
<td>2.06</td>
<td>Normal</td>
<td>49</td>
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</tbody>
</table>

AE, adverse event; HR, hazard ratio; MA, meta-analysis; PCP, Pneumocystis carinii pneumonia; PM, pentamidine; RDI, relative dose intensity; RR, relative risk; TMP/SMZ, trimethoprim/sulfamethoxazole.
Table 2  Cost and utility estimations used in the model

<table>
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<td><strong>Cost (US$)</strong></td>
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<tr>
<td>Cost of prophylaxis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TMP/SMZ daily (80 mg/400 mg)</td>
<td>0.04</td>
<td>0.01</td>
<td>0.95</td>
<td>Gamma</td>
<td>YZ</td>
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<td>PM monthly (300 mg)</td>
<td>24.06</td>
<td>17.65</td>
<td>24.70</td>
<td>Gamma</td>
<td>YZ</td>
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<td>Cost of AEs per event</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Liver dysfunction</td>
<td>144.11</td>
<td>63.64</td>
<td>224.58</td>
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<tr>
<td>Kidney dysfunction</td>
<td>10034.09</td>
<td>5613.72</td>
<td>16699.95</td>
<td>Gamma</td>
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<tr>
<td>Neutropenia</td>
<td>704.50</td>
<td>563.60</td>
<td>845.40</td>
<td>Gamma</td>
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<td>Thrombocytopenia</td>
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<td>1449.00</td>
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<td>Rash</td>
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<td>Electrolyte disturbance</td>
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<td>4305.60</td>
<td>6458.40</td>
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<td><strong>Cost of PCP treatment</strong></td>
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<tr>
<td>PCP recovery</td>
<td>2199.68</td>
<td>532.19</td>
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<td>PCP-related death</td>
<td>24 893.38</td>
<td>19914.70</td>
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<tr>
<td><strong>Cost of chemotherapy</strong></td>
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<td>Imaging tests per cycle</td>
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<td>Lab tests per cycle</td>
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<td>Service fees per cycle</td>
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<td>Cyclophosphamide per mg</td>
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<td>Doxorubicin per mg</td>
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<td>41.77</td>
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<td>YZ</td>
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<tr>
<td>Vincristine per mg</td>
<td>28.27</td>
<td>2.83</td>
<td>28.27</td>
<td>Gamma</td>
<td>YZ</td>
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<tr>
<td>Prednisone per mg</td>
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<td>0.0021</td>
<td>0.064</td>
<td>Gamma</td>
<td>YZ</td>
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<td><strong>Cost of follow-up period</strong></td>
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<td>Re-examination per time</td>
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<td>End-of-life care</td>
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<td><strong>Utility</strong></td>
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<td>Decrement related to AEs</td>
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<tr>
<td>Liver dysfunction</td>
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<td>0.04</td>
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<td>0.11</td>
<td>Beta</td>
<td>37</td>
</tr>
<tr>
<td>Related to PCP</td>
<td>0.61</td>
<td>0.49</td>
<td>0.73</td>
<td>Beta</td>
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<td>Related to chemotherapy</td>
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<td>On treatment</td>
<td>0.82</td>
<td>0.66</td>
<td>0.98</td>
<td>Beta</td>
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<td>Post-treatment within 1 year</td>
<td>0.90</td>
<td>0.72</td>
<td>1.00</td>
<td>Beta</td>
<td>39</td>
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<td>Post-treatment beyond 1 year</td>
<td>0.88</td>
<td>0.70</td>
<td>1.00</td>
<td>Beta</td>
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</tr>
<tr>
<td>Survive without lymphoma</td>
<td>0.88</td>
<td>0.70</td>
<td>1.00</td>
<td>Beta</td>
<td>39</td>
</tr>
</tbody>
</table>

AE, adverse event; PCP, *Pneumocystis carinii* pneumonia; PM, pentamidine; TMP/SMZ, trimethoprim/sulfamethoxazole; YZ, Yaozhi network.
while aerosolised pentamidine 300 mg monthly according to European guideline. Costs for service and tests, management of AEs, PCP treatment, follow-up and end-of-life care were estimated from published literature. The management costs for AEs were the management cost per event multiplied by the corresponding incidence rates. The follow-up schedule was determined according to Chinese clinical practice guideline for lymphoma, which recommended re-examination once every 3 months within the first 2 years, once every 6 months for the third to fifth years and once a year after 5 years and then follow-up for lifelong when the patients with DLBCL were in complete remission after R-CHOP.

All cost estimations were inflated to 2021 values according to the Chinese Healthcare Consumer Price Index (http://data.stats.gov.cn/) and were converted into US dollars (exchange rate: ¥6.45=US$1.00).

**Utility estimations**

Utility values were incorporated in the model to reflect quality of life among different health states. Disutility values for the TMP/SMZ-related AEs were taken into

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Prophylactic medication</th>
<th>PCP occurrence</th>
<th>Prophylaxis</th>
<th>Control</th>
<th>Onset time (days)</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto et al</td>
<td>NHL</td>
<td>TMP/SMZ</td>
<td></td>
<td>0/121</td>
<td>6/176</td>
<td>60 (30–90)</td>
<td>2004–2008</td>
</tr>
<tr>
<td>Hardak et al</td>
<td>DLBCL</td>
<td>TMP/SMZ</td>
<td></td>
<td>0/8</td>
<td>1/39</td>
<td>76 (46–103)</td>
<td>2004–2010</td>
</tr>
<tr>
<td>Kim et al</td>
<td>NHL</td>
<td>NG</td>
<td></td>
<td>0/13</td>
<td>14/700</td>
<td>102 (85–147)</td>
<td>2007–2011</td>
</tr>
<tr>
<td>Lee et al</td>
<td>DLBCL</td>
<td>TMP/SMZ</td>
<td></td>
<td>0/137</td>
<td>33/602</td>
<td>69 (13–188)</td>
<td>2004–2019</td>
</tr>
</tbody>
</table>

DLBCL, diffuse large B-cell lymphoma; NG, not given; NHL, non-Hodgkin’s lymphoma; PCP, Pneumocystis carinii pneumonia; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; TMP/SMZ, trimethoprim/sulfamethoxazole.
The long-term utilities of patients in the first and subsequent years were based on a nationwide study conducted in China.\(^{39}\)

### Model outputs

The outcomes were lifetime costs, life years (LYs) and quality-adjusted life years (QALYs). QALYs were estimated as the duration of time weighted by the utility of each state. We also estimated incremental cost-effectiveness ratios (ICERs), which were calculated as the difference between the costs of the two strategies divided by the difference between their effectiveness. According to Chinese guideline for pharmacoeconomic, the willingness-to-pay (WTP) threshold was set at US$31,315.23 per QALY, which was 3 times the 2021 per capita Chinese gross domestic product. ICER not exceeding the WTP threshold was considered cost-effective. Costs and health utilities were discounted at a rate of 5.0% per year. A half-cycle correction was used in the model.

### Sensitivity analyses

Sensitivity analyses were performed to test the uncertainty of the model. In deterministic sensitivity analysis (DSA), key model parameters were varied separately using reported credible intervals or ±20% of base-case values.

The discount rate ranged from 0% to 8%. Probabilistic sensitivity analysis (PSA) was carried out with 1000 Monte Carlo simulations to capture all parameter uncertainty simultaneously. Base-case value, the variation range and probability distribution of model parameters are shown in table 1 and table 2.

### RESULTS

#### Meta-analysis

**Literature search**

The process of literature screening and selection are presented in figure 2. A total of 661 papers were yielded for the initial screening. There was no RCT for this literature search. After full-text screening, four studies were included to assess the effectiveness of prophylactic TMP/SMZ in NHL treated with R-CHOP21. The references excluded after full-text evaluation and the specific reasons are listed in online supplemental appendix C.

#### Study characteristics and quality

All selected studies used retrospective cohort design. The sample sizes of these studies ranged from 47 to 739. The basic features of the included articles are presented in table 4.

![Figure 3](http://bmjopen.bmj.com/figure3.png)

**Figure 3** Forest plot of meta-analysis on the association between Pneumocystis carinii pneumonia (PCP) prophylaxis and the risk of PCP in non-Hodgkin’s lymphoma.

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**Table 4** Newcastle-Ottawa Quality Assessment Scale for included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Items</th>
<th>Hashimoto et al(^{51})</th>
<th>Hardak et al(^{46})</th>
<th>Kim et al(^{15})</th>
<th>Lee et al(^{8})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection</td>
<td>Representativeness of the exposed cohort</td>
<td>☆</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td></td>
<td>Selection of the non-exposed cohort</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td></td>
<td>Ascertainment of exposure</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td></td>
<td>Demonstration that outcome of interest was not present at start of study</td>
<td>☆</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>Comparability</td>
<td>Comparability of cohorts on the basis of the design or analysis</td>
<td>☆★</td>
<td>☆★</td>
<td>★☆</td>
<td>★☆</td>
</tr>
<tr>
<td>Outcome</td>
<td>Assessment of outcome</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td></td>
<td>Was follow-up long enough for outcomes to occur</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td></td>
<td>Adequacy of follow-up of cohort</td>
<td>★</td>
<td>★</td>
<td>★</td>
<td>★</td>
</tr>
<tr>
<td>Total scores</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>
table 3. The results of the bias risk assessment according to the NOS are displayed in table 4.

Meta-analysis results
Four studies, including 1796 patients, were incorporated in the comparison, and the result revealed that there was a significant reduction in the occurrence of PCP infections in the prophylaxis group compared with control group (0% vs 3.56%; RR 0.17; 95% CI 0.04 to 0.67; p=0.01; figure 3). Not significant heterogeneity was found among studies ($\chi^2=5.09$, p=0.17, $I^2=41\%$) and the fixed-effect model was used. Funnel plot did not show a significant publication bias among included studies (figure 4).

Cost-effectiveness analysis
Base-case analysis
In this analysis, NHL treated with R-CHOP21 with primary prophylaxis produced an additional 0.64 LYs and 0.57 QALYs compared with no prophylaxis. From the Chinese healthcare system perspective, the corresponding costs over lifetime horizon spent for prophylaxis in comparison to no prophylaxis were US$26,114.40 and US$25,586.79, respectively. The ICER for PCP prophylaxis versus no prophylaxis was US$929.25 per QALY, which did not exceed the WTP threshold in China. Details on the base-case results are shown in table 5.

Sensitivity analyses
In DSA, PCP prophylaxis remained cost-effective as the ICERs would not turn out to exceed the WTP threshold when varying the model parameters. The tornado diagram (figure 5) showed that the variable with greatest influence on the ICER was PCP incidence without prophylaxis, followed by the RR of PCP with TMP/SMZ and the management cost of kidney dysfunction. The cost-effectiveness acceptability curves (figure 6) exhibited that the probability of the PCP prophylaxis strategy being cost-effective was 100% at a WTP of US$31,315.23 per QALY.

DISCUSSION
Although a few PCP cases have been reported in clinical trial of rituximab, emerging evidences suggest that PCP is occurring more frequently in patients with lymphoma along with the substantial use of rituximab-containing chemotherapy, especially R-CHOP. Several guidelines recommend to prevent PCP in patients receiving R-CHOP, but there is no consensus on the necessity of universal prophylaxis in patients treated with R-CHOP21 due to that a longer therapy interval might result in a subtle reduction in the incidence of PCP compared with intensive dose of R-CHOP14. Hence, a meta-analysis was performed to clarify the specific effect of PCP prevention in this population. Considering the substantial damage to health as well as the low expenditure of medications for prevention, it is of great significance to assess whether a universal prevention is economically worthwhile for such a low PCP incidence. To our best of knowledge, this study is the first cost-effectiveness analysis considering the value of routine PCP prophylaxis in NHL treated with R-CHOP21. The comprehensive study involves integrating and aggregating clinical data in an epidemiologically reasonable manner to obtain relevant and informative results that are difficult or impossible to obtain otherwise.

The result of meta-analysis revealed that first-line therapy using TMP/SMZ as prophylactic strategy yielded an 83% reduction of PCP incidence without significant heterogeneity. Our result was slightly superior to a prior similar meta-analysis, which showed that TMP/SMZ lowered the incidence of PCP by 72% in patients with lymphoma (RR 0.28; 95% CI 0.09 to 0.94). But the population in the prior study included patients receiving all

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Base-case cost-effectiveness results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strategy</strong></td>
<td><strong>Prophylaxis</strong></td>
</tr>
<tr>
<td>Cost on chemotherapy (US$)</td>
<td>18,070.80</td>
</tr>
<tr>
<td>Cost post chemotherapy (US$)</td>
<td>80,436.60</td>
</tr>
<tr>
<td>Total cost (US$)</td>
<td>26,114.40</td>
</tr>
<tr>
<td>Total LYs</td>
<td>26.96</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>24.12</td>
</tr>
<tr>
<td>ICER per LY (US$)</td>
<td>830.29</td>
</tr>
<tr>
<td>ICER per QALY (US$)</td>
<td>929.25</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.
rituximab-contained regimens, and the total sample size was smaller than the current study, which included one latest study published in 2021 with a sample size of 739 patients. Therefore, this updated meta-analysis yielded a more convinced RR value of PCP prevention for patients with NHL treated with R-CHOP21.

Meanwhile, PCP prophylaxis during R-CHOP21 chemotherapy was demonstrated to have a high probability of being cost-effective at a WTP threshold of US$31 315.23/QALY from Chinese healthcare system perspective. In addition, the DSA revealed that the most influential parameter on the result was PCP incidence without prophylaxis, which is consistent with other cost-effectiveness analysis studies focusing on patients with Wegener’s granulomatosis and Crohn’s disease, suggesting that PCP incidence without prophylaxis is a
crucial parameter in the model. Individuals receiving PCP prophylaxis were expected to have an additional gain of approximately 0.57 QALYs due to mitigation of PCP risk and decline of terminating or delaying R-CHOP chemotherapy. The result suggested that routine PCP prophylaxis avoided morbidity of PCP with an improvement in survival. Given the clinical benefit, low expenditure and easy availability of TMP/SMZ in China, routine prophylaxis for PCP in patients with NHL scheduled to receive R-CHOP21 chemotherapy may be an optimal option. But future study should be needed to better define subgroup of patients with NHL at highest risk of PCP, which is conducive to accurately offer PCP prophylaxis to targeted population.

With the increasing popularity of rituximab use and the attendant increased risk of PCP, questions have arisen about the need for routine PCP prophylaxis for rituximab users. Recently, the effectiveness and tolerable safety profile of PCP primary prophylaxis in patients receiving all rituximab-containing treatments were further confirmed in an observational study, in which NHL constituted a substantial target population. Considering R-CHOP21 is the primary treatment option for NHL, this population was identified for our cost-effectiveness analysis, which could provide insights into the economic value of PCP prophylaxis among R-CHOP21 users.

Several caveats should be kept in mind regarding these results. First, the effectiveness of first-line TMP/SMZ for PCP prophylaxis was generated by our meta-analysis owing to the absence of data in patients with NHL receiving R-CHOP21. The studies included in the meta-analysis were retrospective and limited in number. In addition, the included studies were conducted in the populations of South Korean, Japanese and Israelis, but lack of Chinese population may have potential impact on the results of the cost-effectiveness analysis. However, the DSA was performed by adjusting the preventive effect within reasonable range, which confirmed that variations in preventive effect would not qualitatively change the outcomes of the cost-effectiveness analysis. Future research should place more attention on PCP prevention in NHL. Second, the elevated risk of PCP in patients with lymphoma treated with rituximab-containing chemotherapy are considered to be due to the use of anticancer drugs and multifaceted factors such as male gender, advanced age, lymphopenia (<1000/mL before R-CHOP therapy), more therapy cycles, etc. However, the risk stratification of these factors and other possible factors are yet to be well characterised in patients with NHL, thus hampering the assessment for patients with different characteristics. As such, future cost-effectiveness analysis on risk or other stratifications should be warranted when more data are available. Third, our meta-analysis could not disentangle the effects of varied dosage regimens of TMP/SMZ since different dosages of TMP/SMZ (80 mg/400 mg daily or 160 mg/800 mg twice every week) were applied in publications included in the meta-analysis. A commonly used TMP/SMZ prophylaxis strategy (TMP/SMZ 80 mg/400 mg daily) was chosen in our model, as there is insufficient evidence to indicate that the efficacy of different TMP/SMZ dosages differ. Fourth, the initiation and duration of TMP/SMZ prophylaxis were not consistent in different studies. We evaluated the strategy of PCP prophylaxis synchronised with R-CHOP chemotherapy. More trials are warranted to ascertain the specific strategy of PCP prophylaxis. Fifth, we only evaluated second-line pentamidine when patients were intolerant to first-line medication, because other alternative drugs like dapsone and atovaquone are poorly accessible and sparsely used in China. In addition, results of sensitivity analysis suggested that the efficacy of second-line drugs had little effect on the economic results. Finally, the efficacy of R-CHOP21 on NHL used in the research were derived from the population of DLBCL, which accounts for approximately 40% of adults with NHL in China. The efficacy of different subtypes of NHL might produce biases in model, but the sensitive analysis revealed that the efficacy was not a parameter that mainly affects the ICER. In addition, the extrapolation application to other NHL subtypes might be reasonable, because the incidence of rituximab-related PCP and the prophylaxis efficacy are almost the same in most other NHL subtypes.

CONCLUSION

In conclusion, our findings revealed that prophylactic medication for PCP in NHL receiving R-CHOP21 is highly effective with an RR of 0.17, and routinely initiating chemoprophylaxis against PCP is overwhelmingly cost-effective over no prophylaxis from the Chinese healthcare system perspective. The study might provoke the medical system attention to the rituximab-related PCP again, and the result would provide evidence for decision makers to take more active measures of PCP prevention in patients with NHL undergoing R-CHOP21.

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