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SYSTEMATIC REVIEW

Reporting Quality in Health Economic Evaluation Studies of Immune Checkpoint Inhibitors: A Systematic Review

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Abstract

Background and Objective The introduction of immune checkpoint inhibitors (ICIs) in oncology presents a critical healthcare policy challenge for resource allocation due to their substantial financial burden. This study assessed the reporting quality of health economic evaluation (HEE) studies of ICIs.

Methods This study conducted a systematic literature search of four databases (PubMed, EMBASE, Cochrane CENTRAL, and the International HTA Database) for studies published between January 1, 2014 and December 31, 2022. All ICIs approved up to December 31, 2022, in the USA, EU, China, and Japan were included. Reporting quality was assessed using the Consolidated Health Economic Evaluation Reporting Standards published in 2013 (CHEERS 2013), which is the most widely recognised and implemented reporting guideline for HEE studies. Subgroup analyses were also performed based on the risk of sponsorship bias or citation of CHEERS 2013.

Results A total of 5368 records were identified, 252 of which were included after full-text review. The study design, setting, and ICIs most frequently observed were cost-effectiveness and cost-utility analyses (63.5%), the USA (46.0%), and pembrolizumab (38.1%), respectively. Of the 24 items of CHEERS 2013, fully reported items were limited, particularly in the Methods section. Setting and location were not reported in 94.4% of the records. Subgroup analyses also revealed insufficient reporting of items in the Methods section, particularly "Setting and location".

Conclusion Health economic evaluation studies on ICIs between 2014 and 2022 had limited reporting across the 24 items of CHEERS 2013, regardless of sponsorship bias risk or citations. The items on setting and location in the Methods section were particularly underreported, emphasising the need for transparent reporting in HEE studies of ICIs.

1 Introduction

The economic burden of cancer represents one of the most critical issues in the context of health policy worldwide, along with its huge disease burden [1, 2]. It accounts for large healthcare spending for both patients and insurers, and productivity loss due to employment loss, absenteeism, presenteeism, and premature deaths [2–4]. The economic burden is substantial, as the estimated global cost of cancer from 2020 to 2050 is 25.2 trillion international dollars [2]. Considering the economic impact of cancer care, based on the wide range of cancer economic burdens and finite resources in healthcare systems, it is crucial for policymakers to develop effective policies to manage the expected increase in cancer prevalence and improve morbidity and mortality.

Among the cancer-related economic impacts, an increase in healthcare spending, particularly due to increasing anticancer drug prices, is a major global challenge. Increased anticancer drug prices, although associated

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Key Points

The reporting quality of health economic evaluation (HEE) studies was evaluated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2013) published in 2013. However, the reporting quality of HEEs of immune checkpoint inhibitors (ICIs)—a growing concern in health policy due to the significant economic burden of cancer, remains unclear.

Despite the passage of over a decade since the publication of CHEERS 2013, the reporting quality for HEE studies on ICIs was generally limited. Notably, most studies did not fully adhere to the CHEERS 2013 guidelines in the Methods section, particularly evident in the setting and location items, even in the subgroups stratified by the presence or absence of risk of sponsorship bias or whether the CHEERS 2013 statement was cited.

Transparent reporting is essential for the reproducibility of HEEs. This study highlights the insufficient reporting of CHEERS items among current ICI-related HEE studies, particularly in the Methods section. These findings inform both researchers conducting such evaluations and policymakers referencing ICI HEE studies about critical reporting gaps.

with improvement of cancer-related outcomes, may limit individual treatment access and impact management of resources in healthcare systems [5]. Among the anticancer agents, immune checkpoint inhibitors (ICIs), which are the cornerstone of cancer immunotherapy that have undergone remarkable development over the past two decades, have contributed substantially to growing costs [6, 7]. Evidence shows that expenditures of ICIs increased from 2.8 million to 4.1 billion dollars between 2011 and 2021 in the USA Medicaid Programmes [8]. Multiple factors are responsible for this rapid growth of ICIs. These include (1) the expansion of eligible cancer types and effective combination therapies beyond monotherapy alone [9]; (2) high price points, despite reductions throughout the distribution process [8]. As of 2021, ICIs account for approximately 19.1% of total healthcare spending on anticancer drugs [9, 10]. ICI healthcare spending continues to outpace the growth of overall anticancer drug spending. This proportion is projected to increase to 19.4% by 2025 [9, 10]. Moreover, ICIs offer the potential for extended survival years through superior long-term survival compared to conventional chemotherapy agents [11] However, there are concerns regarding increased cumulative drug costs from prolonged treatment. Additional medical expenses associated with immune-related adverse events are also a concern [12]. Given such financial impacts, ICIs have led to discussions on the necessity of considering economic burden in addition to clinical efficacy.

Health economic evaluations (HEEs), including cost-effectiveness and cost-utility analyses, assess alternative courses of action by comparing their costs and outcomes [13]. The HEEs examine both economic costs and clinical benefits from the perspective of the health sector and society. Well-designed HEEs with clear principles and rigorous methodology can provide policymakers with evidence-based recommendations to help effective resource allocation [14]. Therefore, several countries have used HEE-based guidance from third-party agencies, e.g., the National Institute for Health and Care Excellence (NICE) in the UK, for insurance coverage and/or price adjustment of new health technologies [15]. Along with HEEs from these agencies, numerous HEE studies have been conducted by researchers and manufacturers to help policymakers in decision making [16, 17]. To ensure that HEE can effectively inform policy decision making, it is essential that robust methodologies are applied, valid decision models with appropriate data and assumptions are developed, and a comprehensive evaluation of uncertainty is conducted. These should all be reported in an explicit and transparent manner [16]. However, fully covering these within the limited pages of journals has been challenging, and the reporting of HEE research has long been an issue from the perspective of reporting quality improvement [18].

To address this, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) developed and published reporting standards, i.e., the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [13]. The CHEERS checklist, first published in 2013 and revised in 2022 [13, 19], is available through the Enhancing the Quality and Transparency of Health Research (EQUATOR) network [20]. It has been translated into several languages and is referenced in multiple HEE studies worldwide [21]. To date, there is only one previous systematic review of HEEs of ICIs [22]. However, the review was limited to only six the US Food and Drug Administration (FDA)-approved drugs at the time of the study, including nivolumab, ipilimumab, and pembrolizumab, and did not assess the reporting quality. As of December 31, 2022, more than 20 ICIs have been approved worldwide [23]. Moreover, numerous systematic reviews of HEEs have inappropriately utilised CHEERS as a quantitative assessment tool for methodological quality instead of reporting quality [24–28]. This misapplication of CHEERS can result in incorrect assessments of methodological rigor and transparency in individual HEE studies, which may subsequently impact health policy decisions. Therefore, there is a critical unmet need for an updated systematic review evaluating the reporting quality and appropriate utilisation of CHEERS, which includes

the latest drugs, both in the context of research and health policy.

Owing to the increasing importance of HEEs for ICIs, there is a rising demand from both academic and policy sectors to systematically and appropriately assess the quality of reporting in HEE studies. In this context, this study aimed to systematically review the HEEs of all approved ICIs through 2022 and to assess the quality of reporting using CHEERS.

2 Methods

2.1 Study Design

The research question of this study addresses the reporting adherence to CHEERS of all published HEEs for ICIs approved through 2022. To answer this question, a systematic review was conducted in accordance with the pre-registered protocol in PROSPERO (CRD42023439699). This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [29].

2.2 Inclusion and Exclusion Criteria

Cost-effectiveness, cost-utility, cost-benefit, and cost-minimisation studies for the HEEs of ICIs were included. This study focused on all neoplasms eligible for ICIs, including haematological diseases and sarcomas. A previous systematic review has focused solely on drugs approved by the FDA [22]. However, the development and approval of ICIs outside the USA in recent years have been remarkable. The Cancer Research Institute in the USA provides information on ICIs approved by the FDA, European Medicines Agency (EMA), China's National Medical Products Administration (NMPA), and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) [23]. Considering this, the present study included drugs approved by all four regulatory agencies: FDA, EMA, NMPA, and PMDA. The included ICIs were as follows: atezolizumab, avelumab, cadonilimab, camrelizumab, cemiplimab, dostarlimab, durvalumab, envafolimab, ipilimumab, nivolumab, pembrolizumab, penpulimab, relatlimab, retifanlimab, serplulimab, sintilimab, sugemalimab, tislelizumab, toripalimab, tremelimumab, and zimberelimab. As this study focused on the HEEs of ICIs approved through December 31, 2022, assuming that CHEERS 2022, published in January 2022, had not yet been adequately disseminated to investigators at the time the HEEs of these ICIs were conducted. Therefore, studies that cited the CHEERS 2022 statement were excluded. Publication type was limited to original articles, and language was limited to English [30].

2.3 Search Strategy

Studies from four databases, all of which have been discussed and used by researchers and librarians, were extracted: PubMed, EMBASE, Cochrane CENTRAL, and the International HTA database. As noted above, this study focused on CHEERS 2013 and assumed that it took several months for researchers to adopt CHEERS 2013, published in March 2013, as a reporting standard for HEE studies. Furthermore, the CHEERS 2022 was published in January 2022 [19]. However, considering the process from conducting a study to submission, peer review, and publication, this study assumed that most HEEs published up to December 31, 2022, would adhere to the CHEERS 2013. Therefore, this study defined the search period as January 1, 2014, to December 31, 2022. The search strategies were constructed by two librarians at the authors' institute, and actual searches were conducted on July 7, 2023. The search terms are listed in Supplementary Table 1.

2.4 Study Selection and Data Extraction

After excluding duplicate records, three independent pairs of researchers (SA and TY, SA and SF, and SA and TI) screened the titles and abstracts of the articles found in the literature search. The same pairs of researchers independently screened the full text of each study. After screening the full-text records, the same independent pairs of researchers used pre-specified data extraction forms to collect data from the included HEE studies. Any disagreements were resolved through consensus discussions.

The extracted data included general information and the quality of reporting. General information included study design, setting, target population, intervention (i.e., ICIs), study perspective, time horizon, publication year, risk of sponsorship bias, and citation of CHEERS 2013. The risk of sponsorship bias was defined as present if the authors of the study included employees of the manufacturer or if they received funding from the manufacturer. The quality of reporting will be described independently later.

2.5 Outcome (Reporting Quality)

The outcome of interest was the reporting quality. The quality of reporting among the included studies was evaluated using the CHEERS 2013 checklist [31]. CHEERS 2013 includes 24 items divided into six main categories to provide systematic reporting of HEEs. With reference to CHEERS 2013, several items required reporting of multiple aspects (e.g., item 2: "Provide a structured summary of the objectives, perspective, setting, methods [including study design and inputs], results [including base case and uncertainty analyses], and

conclusions"). To distinguish between full and partial reporting of these components, a unique checklist based on CHEERS 2013 was developed (Supplementary Table 2). Studies were assessed as "fully reported" if they met all checklist items, "partially reported" if only some were met, "not reported" if none were met, and "not applicable" if irrelevant.

2.6 Statistical Analysis

First, the characteristics of the included studies were summarised as numbers and proportions (%) of categorical variables. The annual publication numbers of the studies, distinguishing them based on whether the CHEERS statement was cited, were also described. Then the quality of reporting results by presenting the numbers of the categorical outcome variables ("fully reported," "partially reported," and "not reported") for each of the 24 items was described. This study assumed that the quality of reporting might differ by the presence of industry sponsorship [32]. Furthermore, this study assumed that a declaration to follow CHEERS 2013 and citing the statement may influence the researcher's attitude toward transparent reporting. Given this, subgroup analyses that presented the proportions of "fully reported" outcomes among all outcome variables excluding "not applicable" for each item by the presence of "risk of sponsorship bias" or "citation of CHEERS 2013" were performed.

3 Results

A flow diagram of the study is shown in Fig. 1. Of the 5368 records, 344 were eligible after the screening of titles and abstracts. Of the 344 records, 252 were finally included, after full-text screening. A summary of the included studies is presented in Supplementary Table 3.

Table 1 shows the baseline characteristics of the records. Of the 252 records, 160 (63.5%) were subjected to the cost-effectiveness and cost-utility analyses. The settings were mostly in the USA (n = 116, 46.0%) and China (n = 66, 26.2%). Non-small cell lung cancer (n = 83, 32.9%), melanoma (n = 31, 12.3%), and renal cell carcinoma (n = 28, 11.1%) were the most common disease areas. The most common interventions (i.e., ICIs) were pembrolizumab (n = 96, 38.1%), nivolumab (n = 44, 17.5%), and atezolizumab (n = 36, 14.3%). Most studies were conducted from a payer's perspective (n = 227, 90.1%) and non-lifetime horizons (n = 148, 58.7%). Eighty-four studies (33.3%) were at risk of sponsorship bias, and only 37 (14.7%) cited CHEERS 2013. As shown in Fig. 2, the number of publications showed an annual increase, and the proportion of CHEERS 2013 citations showed a substantial increase from 2021.

The overall quality of reporting for the study is shown in Fig. 3. Of the 24 items, the most "fully reported" items were frequently observed for the "Title and abstract," "Results," and "Other" (except "source of funding") sections (e.g., title [n = 244, 96.8%], estimating resources and costs [n = 237, 94.0%], study parameters [n = 231, 91.7%], incremental costs and outcomes [n = 248, 98.4%], characterising uncertainty [n = 235, 93.3%], and conflicts of interest [n = 249, 98.8%]). In contrast, the least "fully reported" items were observed in the "Methods" section (e.g., setting and location [n = 14, 5.6%], study perspective [n = 94, 37.3%], choice of health outcomes [n = 75, 29.8%], measurement of effectiveness [n = 80, 31.7%], analytic methods [n = 55, 21.8%], and source of funding [n = 87, 34.5%]). Of the least "fully reported" items, setting and location were predominantly "not reported" (n = 238, 94.4%).

The results of subgroup analyses are shown in Figs. 4 and 5. Similar to the results for the overall studies, the most "fully reported" items were observed in the "Title and abstract," "Results," and "Other" (except "source of funding") sections, whereas the least "fully reported" items were observed in the Methods section for both subgroup analyses. The HEE studies at the risk of sponsorship bias were more likely to report the measurement and valuation of preference-based outcomes (present, 75.9% vs absent, 29.5%) and assumptions (present, 70.2% vs absent, 40.5%), whereas they were unlikely to report the choice of health outcomes (present, 15.5% vs absent, 36.9%). Interestingly, studies with a risk of sponsorship bias had a higher proportion of "fully reported" for the "source of funding" item compared to those without, although both proportions were low (present, 38.1% vs absent, 32.7%) (Fig. 4). Focusing on the citations of CHEERS 2013, HEE studies with citations were more likely to report many of the CHEERS 2013 items than those without. Among the items, the choice of health outcomes (cited, 51.4% vs not cited, 26.0%) and the measurement of effectiveness (cited, 43.2% vs not cited, 29.8%) adhered well (Fig. 5).

4 Discussion

In this systematic review, 252 HEE studies on ICIs were identified between 2014 and 2022. The number of published studies has shown an annual increase, and the proportion of CHEERS 2013 citations increased in 2021 and 2022 compared to the pre-2020 period. The reporting quality, evaluated by CHEERS 2013, was generally limited. For example, "fully reported" items were limited, observed only for the "Title and abstract," "Results," and "Other" (except "source of funding") sections among the 24 items of CHEERS 2013. The least "fully reported" items were

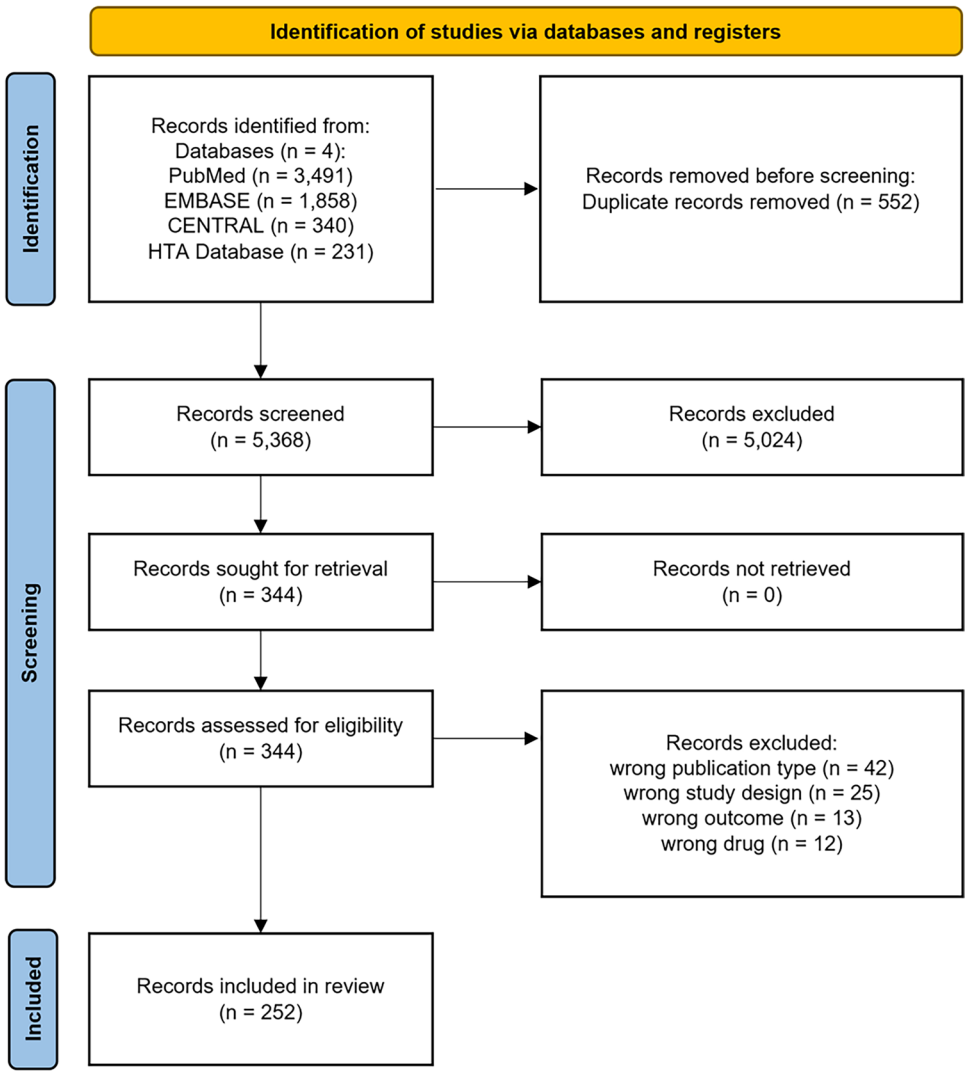

Fig. 1 PRISMA 2020 flow diagram. *PRISMA 2020* the Preferred Reporting Items for Systematic reviews and Meta-Analyses updated in 2020

observed in the "Methods" section, and the item of setting and location was poorly adhered to. The reporting characteristics showed a limited number of items meeting the criteria for "fully reported", particularly within the "Methods" section. Poor adherence to "Setting and location" was especially notable. These patterns persisted even after stratification by the risk of sponsorship bias or citation of CHEERS 2013. In the analyses based on the presence or absence of sponsorship bias risk, some variations in adherence to specific items in CHEERS 2013 were observed. However, studies that cited CHEERS 2013 generally had high adherence to most items compared with studies that did not cite this statement.

Several characteristics were observed in this study, and the potential mechanisms were considered for each. First, many of the included studies used both cost-effectiveness and cost-utility designs from a payer's perspective and were from the USA or China. These countries have large populations eligible for ICI treatment [2]. They also lack national HEE agencies for reimbursement and pricing decisions. This environment may motivate researchers and manufacturers to publish HEE studies to inform policymakers about resource allocation. Second, the number of studies citing CHEERS 2013 remained limited, even though the number of HEE studies on ICIs has increased annually. The CHEERS 2013 statement may not be well received by researchers conducting HEE studies on ICIs. Evidence indicates that more than 80% of PubMed-indexed pharmacoeconomic studies published between 2021 and 2022 did not declare adherence to the CHEERS statement [33]. Third, several of the methodological items were only partially reported. In particular, the settings and locations were often not reported at all. This may indicate that researchers do not sufficiently value the country adjustment emphasised by Drummond et al. [18]. Such adjustment is necessary for discussing the transferability of results [34]. Transparent reporting of setting and location is crucial for improving transferability in policy decision making. For instance, in HEEs of COVID-19

Table 1 Baseline characteristics

$n = 252$ Characteristics	Value
Study design, n (%)	
Cost-effectiveness and cost-utility analyses	160 (63.5)
Cost-utility analysis	69 (27.4)
Cost-effectiveness, cost-utility, and cost-benefit analyses	13 (5.2)
Cost-effectiveness analysis	5 (2.0)
Others	5 (2.0)
Setting, n (%)	
USA	116 (46.0)
China	66 (26.2)
USA and China	12 (4.8)
Others	50 (19.8)
Not reported	8 (3.2)
Target population, n (%)	
Non-small cell lung cancer	83 (32.9)
Melanoma	31 (12.3)
Renal cell carcinoma	28 (11.1)
Oesophageal cancer	20 (7.9)
Others	90 (35.7)
Intervention[a]*, n (%)*	
Pembrolizumab	96 (38.1)
Nivolumab	44 (17.5)
Atezolizumab	36 (14.3)
Ipilimumab + nivolumab	30 (11.9)
Others	71 (28.2)
Study perspective, n (%)	
Payer's perspective	227 (90.1)
Societal perspective	12 (4.8)
Others	5 (2.0)
Not reported	8 (3.2)
Time horizon, n (%)	
Lifetime	90 (35.7)
Non-lifetime	148 (58.7)
Not reported	14 (5.6)
Risk of sponsorship bias, n (%)	
Present	84 (33.3)
Absent	168 (66.7)
Citation of the CHEERS statement, n (%)	
Cited	37 (14.7)
Not cited	215 (85.3)

CHEERS 2013 the Consolidated Health Economic Evaluation Reporting Standards published in 2013

[a]Some of the included reports conducted health economic evaluations of multiple checkpoint inhibitors within multiple arms. Consequently, the total number of interventions exceeded the total sample size (n = 252), resulting in the sum of the percentages exceeding 100%

prevention and treatment, resource utilisation considerations vary significantly across countries and timeframes, including baseline pre-test probability and disease severity, which are influenced by differences in lockdown policies and vaccination coverage rates [35]. Additionally, incomplete reporting of study perspective, choice of health outcomes, measurement of effectiveness, analytic methods, and source of funding is noteworthy. These items are essential for evaluating analytical validity. For instance, study perspective is crucial for identifying the scope of relevant costs and elements, while measurement of effectiveness enables bias quantification through cited effect sizes and their sources. Analytic methods reveal modelling assumptions for validity assessment [13]. Underreporting of these elements limits methodological evaluation. It also complicates policymakers' assessment of HEE transferability. Fourth, even in the presence of the risk of sponsorship bias, there were several items for which the transparency of methodological reporting was high. Manufacturers submit HEE analyses to third-party agencies like NICE for reimbursement and pricing decisions, either concurrent with or prior to published HEE studies [36, 37]. These agency submissions, unrestricted by page limits, allow for more comprehensive reporting. Manufacturers may adapt these agency submissions for published HEE studies. This could explain the higher reporting transparency in manufacturer-sponsored studies. However, it might also indicate potential sponsorship bias. Fifth, although not statistically tested, studies citing the CHEERS 2013 statement were found to have more "fully reported" items than those that did not. However, this number was limited. Authors citing CHEERS 2013 are more likely to have reviewed the checklist compared to those who did not cite CHEERS 2013. Despite this, the fact that only a limited number of items were adhered to suggests that authors citing CHEERS 2013 may have done so as a formality rather than out of recognition of the importance of transparency.

To date, several systematic reviews have evaluated the quality of reporting using the CHEERS 2013 statement. Tai et al used CHEERS 2013 in their systematic review of HEEs conducted from a patient's perspective [24]. In their study, CHEERS 2013 was evaluated using four categories for each item: "fully satisfied (FS)," "partially satisfied (PS)," "not satisfied (NS)," and "not applicable (NA)" The results showing a prevalence of "PS" or "NS" in several items in the Methods section were similar to our findings, although "setting and location" was fully categorised as "FS", unlike in the present study. Similar systematic reviews evaluating reporting quality using CHEERS 2013 have been conducted in various fields, including oncology, cardiology, neurology, plastic surgery, and artificial intelligence in healthcare [25–28, 38]. Some of them also reported adherence to each item of CHEERS 2013, and similar characteristics, e.g., insufficient reporting in the Methods section, such as the study by Tai et al, were observed [26, 27]. For example, Gorry et al conducted a systematic review of HEEs on systemic therapies for advanced melanoma [38]. Their

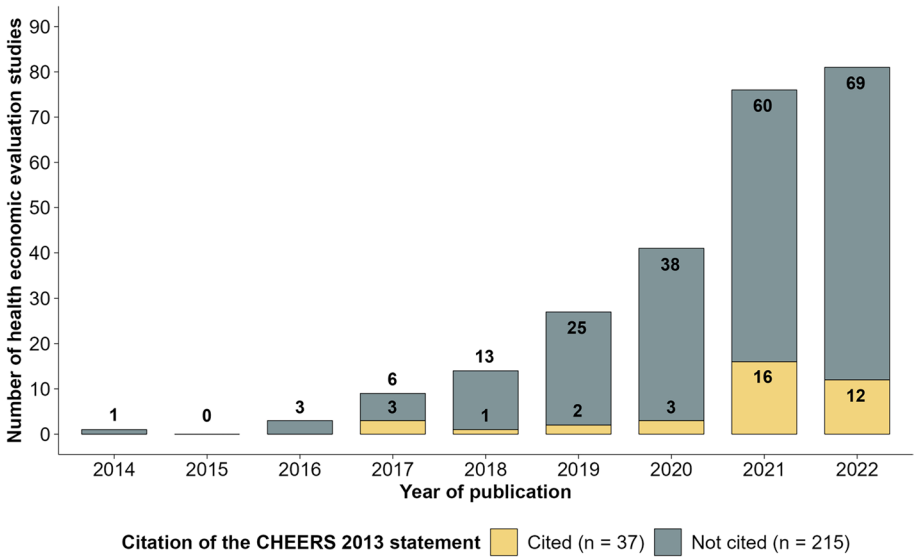

Fig. 2 Number of health economic evaluations stratified by whether CHEERS 2013 was cited. *CHEERS 2013* the Consolidated Health Economic Evaluation Reporting Standards published in 2013

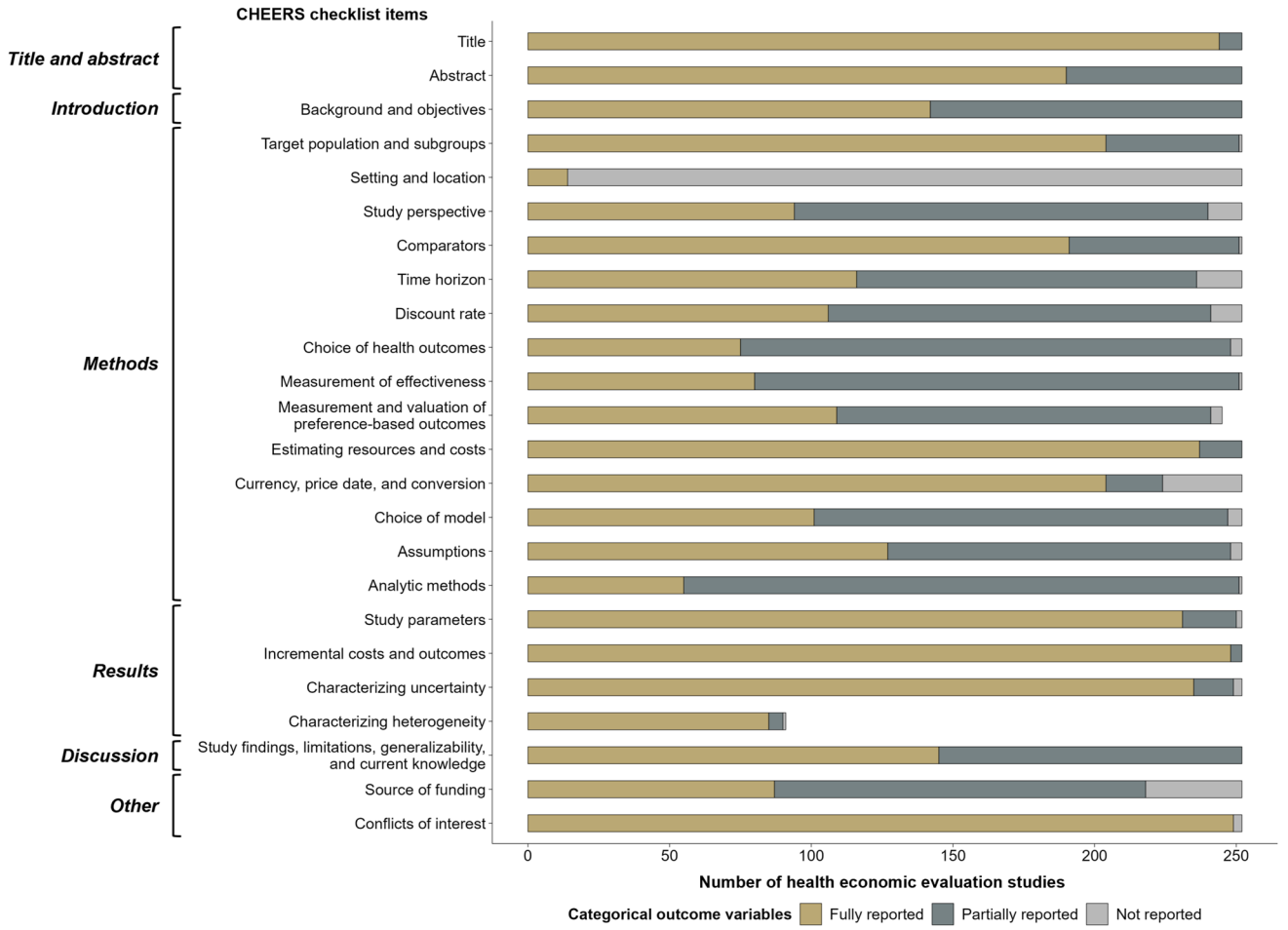

Fig. 3 Reporting quality of health economic evaluation studies according to the CHEERS 2013 checklist. *CHEERS 2013* the Consolidated Health Economic Evaluation Reporting Standards published in 2013

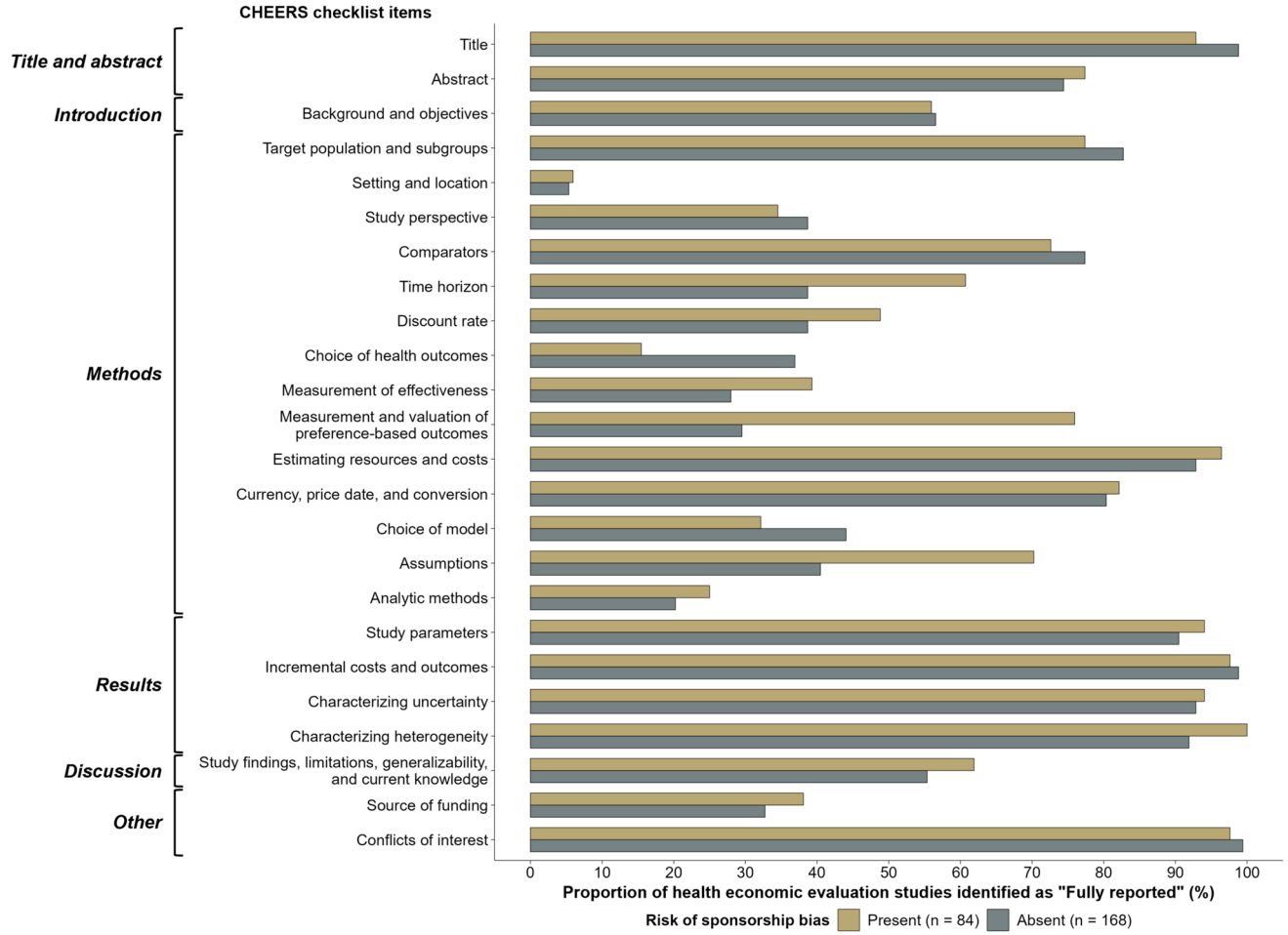

Fig. 4 Proportions of the "fully reported" category classified into the presence or absence of the risk of sponsorship bias. *CHEERS 2013* the Consolidated Health Economic Evaluation Reporting Standards published in 2013. Studies classified as "not applicable" were excluded from description. Specifically, seven studies were excluded from the "measurement and valuation of preference-based outcomes" item (five from "present" and two from "absent" groups), and 161 studies were excluded from the "characterising heterogeneity" item (67 from "present" and 94 from "absent" groups)

study found insufficient reporting of "Setting and location" and "Assumptions" items, aligning with our findings. The insufficient adherence to the "Setting and location" item is consistent with our findings. This may be attributed to the predominance of clinical medicine specialists among authors and reviewers. The clinical medical journals where they typically submit and review manuscripts primarily publish observational studies, randomised controlled trials, and systematic reviews. The reporting guidelines for these research designs—STROBE [39], CONSORT [40], and PRISMA [29]—do not include items comparable to CHEERS' "setting and location". Therefore, adherence to such items may not be standard practice for these specialists. However, unlike our results, they found insufficient reporting of "Characterising heterogeneity" and "Currency, price date, and conversion" items. These differences might be attributed to their focus on advanced melanoma studies from 2000 to 2013, a different timeframe and disease scope, and potential variations in reviewer assessment criteria. All of these studies commonly used CHEERS 2013; however, they share common features. First, adherence to each item was dichotomised into binary values of presence or absence. However, as described in the Methods section, some items encompass multiple assessment dimensions, thereby reducing the binary approach to representing the quality of reporting. Second, all studies consistently defined a total score and used CHEERS 2013 as an assessment tool for reporting quality indicators for each included study. However, the CHEERS 2022 statement strongly discourages such an application of CHEERS, noting that CHEERS was not developed as a scoring tool and that such misuse could lead to misleading interpretations of the results [41]. Our study was carefully designed to address these two concerns commonly observed in previous systematic reviews of reporting quality. In terms of HEEs of

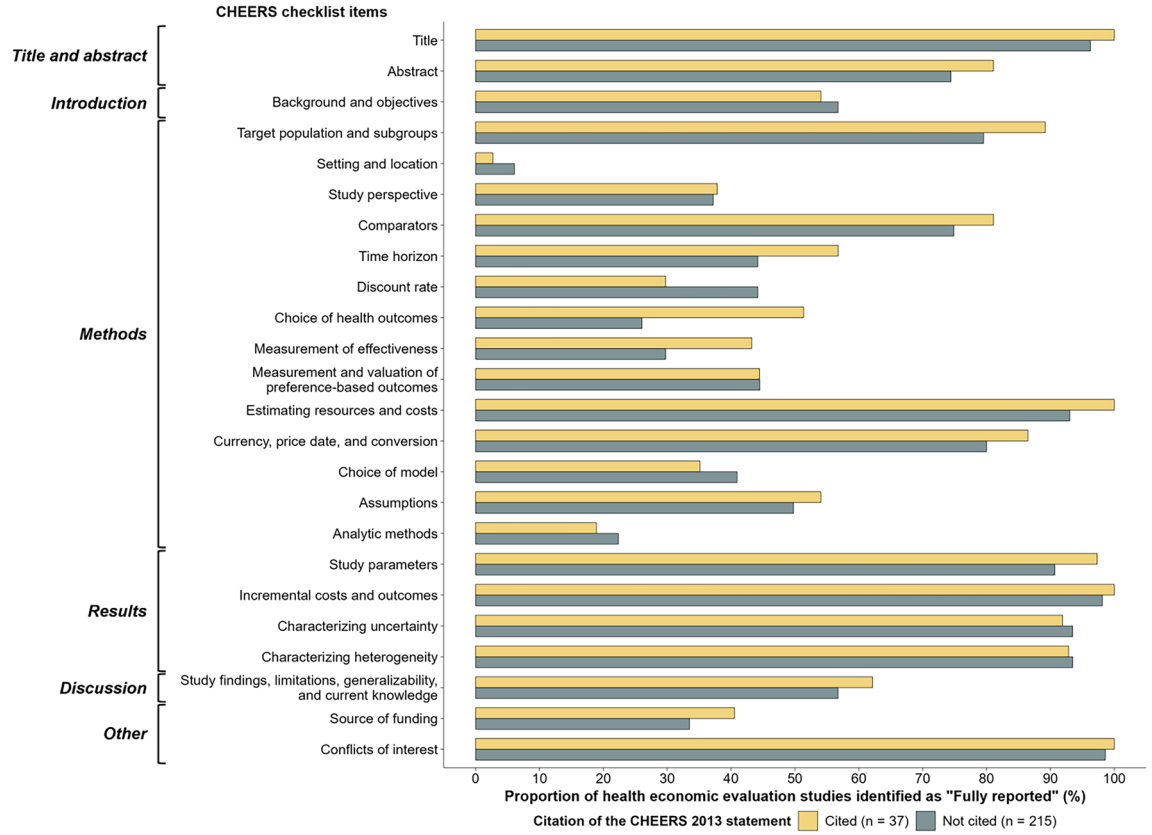

Fig. 5 Proportions of the "fully reported" category were classified according to whether or not the CHEERS 2013 statement was cited. *CHEERS 2013* the Consolidated Health Economic Evaluation Reporting Standards published in 2013. Studies classified as "not applicable" were excluded from description. Specifically, seven studies were excluded from the "measurement and valuation of preference-based outcomes" item (one from "cited" and six from "not cited" groups), and 161 studies were excluded from the "characterising heterogeneity" item (23 from "cited" and 138 from "not cited" groups)

ICIs, only one systematic review was found [22]. However, this systematic review included HEEs of ICIs published up to April 2018, and only three ICIs were included, i.e., nivolumab, pembrolizumab, and atezolizumab. Moreover, only 30 HEEs were included, representing approximately 12% of our study. The quality of reporting was not assessed, suggesting that the quality of reporting in the HEEs of ICIs remains unclear. Taken together, this is the first study to systematically review HEE studies on ICIs and assess their reporting quality.

Our study had several strengths. First, this systematic review was conducted using a rigorous methodology. This included the development of a prespecified protocol and the registration with PROSPERO. Two librarians developed the search strategies. They used four major databases that are important for a comprehensive search of HEE studies. In addition, screening, data extraction, and analyses were performed according to the Cochrane Handbook methodology. This represents the current methodological standard for systematic reviews [42]. Therefore, high reproducibility of the results is expected. Second, the comprehensiveness of the results is expected to be high despite the fact that the search period started in January 2014. The first ICI, nivolumab, was approved by the FDA in December 2014. This was approximately one year after the start of our search period. This may be supported by the fact that only one HEE study on ICIs was identified between 2014 and 2015. Third, adding a "partially reported" category to the CHEERS 2013 items is also a strength. This allowed for a clearer understanding of the extent to which the researchers adhered to each item in the CHEERS 2013 statement. In addition, not using the CHEERS statement as a scoring tool, a common form of "misuse" emphasised in CHEERS 2022 [41], can also be considered a strength.

Our study has several limitations. First, the results were limited to the HEEs of ICIs and cannot be extrapolated to all anticancer drugs or HEE studies. However, the insufficient reporting of the "Setting and location" item may occur due to the predominance of clinical specialists among HEE study authors and manuscript reviewers. If this is true, similar results might be observed for other anticancer drugs. This requires verification in future research. Second, this study

did not examine adherence to or citation of CHEERS 2022. Future research should assess CHEERS 2022 compliance in HEE studies of ICIs published after January 2023. This assessment should utilise a methodology similar to ours. For instance, Sharma et al conducted a systematic review of HEEs in advanced and metastatic gastric cancer using CHEERS 2022 [43]. Their study included publications before January 2023. It demonstrated insufficient reporting in the Methods section, similar to our findings. It may serve as a relevant reference for future work. Third, this study only assessed the quality of reporting and not the quality of the research methodology itself. Policymakers need evaluation methodologies to consider reimbursements and price adjustments. However, transparent reporting is first necessary to properly examine these methodologies. Therefore, future studies may need to assess the methodological quality of HEE studies on ICIs using quality standards such as the CHEQUE tool [44]. Notably, modelling components, fundamental for analytical validity, are crucial, as evidenced by their highest weighted scores in both reporting and methodological quality domains of the CHEQUE tool.

This study has a clear implication: it highlights the importance of comprehensive reporting of items such as methods, which were frequently underreported in this study, for researchers conducting HEE studies on ICIs. Specifically, "setting and location" was largely underreported in this study, although it was crucial to the transferability of the results. Transparent reporting is essential for reproducibility in HEE studies. Only with reproducible results can policymakers and healthcare practitioners assess the reliability and validity of research findings to inform healthcare resource allocation decisions [19]. Therefore, policymakers in countries that use HEE studies for reimbursement and price adjustment might contribute to enhancing the transparency of future HEE research by referring to HEEs from HEE agencies in other countries, such as NICE, and by requiring adherence to reporting guidelines like CHEERS.

5 Conclusion

In this systematic review of 252 HEE studies on ICIs from 2014 to 2022, comprehensive reporting was generally limited to the 24 items included in the CHEERS 2013 statement, regardless of the risk of sponsorship bias or citation of CHEERS 2013. The "setting and location" item in the Methods section was particularly underreported. This study highlights the importance of transparent reporting in HEE studies of ICIs.

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Declarations

Data availability statement The data that support the findings of this study are available from the corresponding author, TY, upon reasonable request.

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