frontiers | Research Topics

Pharmacoeconomics in the area of health technology assessment and outcomes research to prioritize resource use, innovation and investment

Edited by
François R. Girardin, Isabelle Durand-Zaleski, Karen Cohen and Matthias Schwenkglenks

Published in
Frontiers in Pharmacology

ISSN 1664-8714
ISBN 978-2-8325-2595-1
DOI 10.3389/978-2-8325-2595-1

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Pharmacoeconomics in the area of health technology assessment and outcomes research to prioritize resource use, innovation and investment

Topic editors

François R. Girardin — Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland
Isabelle Durand-Zaleski — Assistance Publique Hopitaux De Paris, France
Karen Cohen — University of Cape Town, South Africa
Matthias Schwenkglenks — University of Basel, Switzerland

Citation

Girardin, F. R., Durand-Zaleski, I., Cohen, K., Schwenkglenks, M., eds. (2023). *Pharmacoeconomics in the area of health technology assessment and outcomes research to prioritize resource use, innovation and investment*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-2595-1

Table of contents

frontiers | Frontiers in Pharmacology

TYPE Editorial
PUBLISHED 16 May 2023
DOI 10.3389/fphar.2023.1210002

OPEN ACCESS

EDITED AND REVIEWED BY
Brian Godman,
University of Strathclyde, United Kingdom

*CORRESPONDENCE
François R. Girardin,
francois.girardin@chuv.ch

RECEIVED 21 April 2023
ACCEPTED 10 May 2023
PUBLISHED 16 May 2023

CITATION
Girardin FR, Cohen K, Schwenkglenks M and Durand-Zaleski I (2023), Editorial: Pharmacoeconomics in the era of health technology assessment and outcomes research to prioritize resource use, innovation and investment.
Front. Pharmacol. 14:1210002.
doi: 10.3389/fphar.2023.1210002

Editorial: Pharmacoeconomics in the era of health technology assessment and outcomes research to prioritize resource use, innovation and investment

François R. Girardin[1]*, Karen Cohen[2], Matthias Schwenkglenks[3,4] and Isabelle Durand-Zaleski[5]

[1]Division of Clinical Pharmacology, Department of Laboratory Medicine and Pathology, Faculty of Medicine, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland, [2]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa, [3]Institute of Pharmaceutical Medicine (ECPM), University of Basel, Basel, Switzerland, [4]Epidemiology, Biostatistics, and Prevention Institute, University of Zurich, Zürich, Switzerland, [5]Université Paris Est Créteil, AP-HP URCEco Hôtel Dieu, Paris, France

KEYWORDS

pharmacoeconomics, health technology assessment (HTA), patient related outcome, disinvestment choices, cost-effectiveness

Editorial on the Research Topic
Pharmacoeconomics in the era of health technology assessment and outcomes research to prioritize resource use, innovation and investment

Health economic evaluations in health technology assessment (HTA) focus on balancing the costs and expected benefits of interventions compared to the use of standard-of-care to leverage value to patients and healthcare payers. Pharmaco-economic (PE) studies, in particular, assess the therapeutic value of medical technologies, such as drugs or devices, and encompass multidimensional aspects, e.g., assessments of mutually exclusive drugs options, combination with pre-emptive pharmaco-genetic (PGx) testing to limit adverse reactions, or therapeutic drug monitoring as a precision medicine procedure. The extent to which findings of PE evaluations are translated into informed policy decisions depend on national healthcare systems and population expectations.

PE evaluations have the potential to streamline decision making and innovation in a wide range of therapeutic areas by determining whether the expense incurred by novel treatments is worthwhile, given the willingness-to-pay for health gains achieved, for example, measured as quality-adjusted life-years (QALY). The QALY conceptual framework was first introduced in the 1960s in studies on chronic renal failure (Klarmann et al., 1968): authors reported that the quality-of-life (QoL) with kidney transplant was 25% higher than that with dialysis. The cost per life-year gained by different therapeutic options was estimated with and without the quality adjustment. More than 50 years later, despite the inherent limitations and ethical issues, the QALY remains the most validated metric and generic measure of health to quantify the expected benefit in clinical studies.

Several instruments were developed to complement QALY metrics, such as descriptive disease-specific patient-reported outcomes (PRO), which have better face validity for clinicians. PROs provide unique insight into the outcomes of therapeutic interventions that are important to patients: they are derived from validated descriptive instruments, generic or disease-specific, which are adapted to languages and countries. The results are context specific: one should be cautious when applying them to different settings, as findings may not be transferable to other healthcare systems.

In an article on kidney transplantation, Girardin et al. analyzed the association between immunosuppressant medications and the QoL outcomes in 558 kidney transplant recipients in France, Germany, Spain, and Switzerland. VAS scores and EQ-5D utility scores were adjusted for patient characteristics and medical history. Both elicitation instruments delivered sound results for QoL in kidney transplant patients. Most patients received tacrolimus and mycophenolate mofetil in all four countries. During one-year of follow-up, a significant proportion of patients switched immunosuppressive therapy (according to country, from 20% to 40%), which was associated with worse QoL, irrespective of the initial medications. Although initial treatments were comparable, patient characteristics and evolving trends differed across countries more than between centers.

Several articles in our Research Topic address Research Topic in oncology, where emerging, expensive therapies have received much attention in recent years. Concerns on the clinical side include market entries on the basis of immature data on hard patient outcomes, most importantly overall survival (Prasad et al., 2015) (Paoletti et al., 2020), but also limited understanding of patient perceptions. Incorporating PROs in drug labels has been proposed as a means of giving more weight to cancer patient perspectives in regulatory decisions. A review of Food and Drug Administration (FDA) and European Medicines Agency (EMA) oncology drug labels by Cella et al. revealed relevant limitations and inconsistencies with respect to PRO inclusion, even potential biases towards positive outcomes. This indicates a need for improved and more harmonized guidance, to better inform drug prescribers and users.

Budget constraints are a common issue in most healthcare systems. While the prices of new oncology drugs are matter of growing concern even in high income countries (Godman et al., 2021), low- and middle-income countries, struggle with the costs of oncology drugs despite international price differentials (Al-Ziftawi et al., 2021). These issues are aggravated by restricted population access due to lack of universal healthcare coverage. Locally developed drugs may in some cases contribute to affordability, thus easing the economic burden on patients and their families. The work of You et al. exemplified this concern: the authors found that adebrelimab, an immune checkpoint inhibitor (ICI) developed in China as IgG4 monoclonal antibody against PD-L1, may be a cost-effective option for first-line treatment of extensive-stage small cell lung cancer, from the perspective of the Chinese healthcare system, even though earlier studies found other ICI not to be cost-effective in this indication in China. Lack of cost-effectiveness, partially driven by high drug prices and in some cases limited value for patients (Pontes et al., 2020), also occurs in industrialized countries. In the US study, Li et al. concluded that nivolumab (another ICI) is not cost-effective compared to sorafenib as a first-line therapy for advanced hepatocellular carcinoma. There were hints at cost-effectiveness differences between patient subgroups, specifically in patients with intermediate-stage disease (Barcelona Clinic Liver Cancer stage B).

Heart failure (HF) is an increasing health concern that imposes high costs and resource use. HF management stems from the use of highly cost-effective angiotensin converting enzyme inhibitors (ACEi) and β-blockers to the use of novel medication targets, such as ivabradine, vericiguat, or sodium-glucose cotransporter-2 inhibitors (SGLT2i) dapagliflozin and empagliflozin. Lim et al. reviewed pharmacoeconomic and cost-effectiveness studies of SGLT2i, ARNi, ivabradine, vericiguat, and omecamtiv. Pharmaco-economic analyses of empagliflozin in HF patients with Type 2 diabetes and dapagliflozin for HF with reduced ejection fraction remained below the willingness-to-pay thresholds in most middle- and high-income countries. Still, vericiguat was found cost effective at a higher cost per QALY threshold than SGLT2i. The authors concluded that although cost-effectiveness on newer medications, such as SGLT2i, ARNi, ivabradine, vericiguat, and omecamtiv in HF with reduced ejection fraction is established, there is still lower evidence for their use in HF with preserved ejection fraction that accounts for the majority of HF. Eventually, in low- and middle-income countries, the fundamental recommendation would be that patients be diagnosed early and treated with multiple, sourced renin-angiotensin drugs that remain highly effective and inexpensive rather than with expensive and *a priori* cutting-edge drugs.

Effectiveness and cost-effectiveness evaluation may be particularly challenging when pre-emptive measures are considered, such as pharmacogenomics (PGx) applied to prevent gene-drug related adverse reactions. Van der Wouden et al. found that nation-wide adoption of PGx-guided initial dose and medication selection of single actionable drug-gene interactions could potentially avoid fatal outcomes in 0.3% of patients taking medications such as clopidogrel, capecitabine, 5-FU, thiopurines or irinotecan: the expected cost would be €51000 per prevented death. Still, the evaluation of surrogate endpoints due to wrong drug selections or dosages remain a complex process that must be validated by probabilistic approaches and sophisticated statistic frameworks to address strong assumptions and uncertainty (Buyse et al., 2016; Ciani et al., 2022). Despite no manuscript was submitted in this field, gene therapies for patients with orphan diseases remain a key concern when developing cost-effectiveness decision-models, given the uncertainty in several situations and the enormous pressures put on health authorities to fund any new medicine in this area despite high prices (Luzzatto et al., 2018).

Ninomyia et al. explored a PGx-informed clozapine therapy and blood monitoring schedule based on novel SLCO1B3-SCLO1B7 variants in addition to HLA variants to leverage genotyping test sensitivity for the detection of clozapine-induced agranulocytosis and granulocytopenia (CIAG). By adding SLCO variants, the expected test sensitivity increased, whereas the specificity decreased (89.0%–86.9%) still increasing the overall risk predictability (Ninomiya et al.). Incorporating new SLCO variants to pre-emptively assess CIAG risk improved the effectiveness of PGx-guided clozapine administration: SNP-based predictive tests differ between ancestral groups due to alleles or haplotypes frequencies and varying patterns of linkage disequilibrium (Islam et al., 2022).

New diagnostic tests and drugs are being developed and tested as shown in the clinical articles published in this issue. They offer additional health benefits, which often require additional healthcare resources to be committed at a certain cost (Darlington et al.). To ensure patient access to these novel medications and diagnostic technologies, and to secure the sustainability of healthcare systems, several routes are explored. In addition to increasing the resources committed to healthcare (which is happening in most countries), reducing unnecessary care, and considering decremental cost-effective strategies are current options. The use of PGx allows to reduce risks as shown in two articles published in this issue: the implementation of molecular diagnostics should better identify the most suitable target populations for drugs and reduce overuse. A step further is the consideration of decremental cost-effective strategies. These become relevant in situations where a small health loss can be acceptable in exchange for a large monetary gain reallocated to the healthcare system. Methodologically, related studies follow similar principles as non-inferiority studies, which define an inferior margin of difference, yet acceptable, for therapeutic innovations *versus* the standard-of-care. The development of non-inferiority studies in recent years offers a range of possibilities for economic studies that would identify areas for disinvestment. However, transforming those studies into policies necessitates reassurance that the money saved will be efficiently used for the provision of healthcare. It might also be necessary to provide financial incentives to both health professionals and patients to overcome resistance to change or loss of revenue. For instance, different types of incentives are currently in place to limit the resource use related to medications, with positive incitements for physicians, pharmacists, and patients to foster the use of generic drugs or biosimilars.

Ultimately, HTA and PE could be considered foundation not only for outcome research, but also for comparative research regarding future innovations and investments in the development of precision medicine and personalized therapies.

The editors of the Research Topic would like to thank all the participating contributors for their valuable involvement in the success of the issue on HTA and PE.

Author contributions

FG: writing-draft preparation–submission; KC: reviewing; MS: writing–reviewing; ID-Z: writing–reviewing. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Al-Ziftawi, N. H., Shafie, A. A., and Mohamed Ibrahim, M. I. (2021). Cost-effectiveness analyses of breast cancer medications use in developing countries: A systematic review. *Expert Rev. Pharmacoecon Outcomes Res.* 21, 655–666. doi:10.1080/14737167.2020.1794826

Buyse, M., Molenberghs, G., Paoletti, X., Oba, K., Alonso, A., Van Der Elstw., et al. (2016). Statistical evaluation of surrogate endpoints with examples from cancer clinical trials. *Biom J.* 58, 104–132. doi:10.1002/bimj.201400049

Ciani, O., Grigore, B., and Taylor, R. S. (2022). Development of a framework and decision tool for the evaluation of health technologies based on surrogate endpoint evidence. *Health Econ.* 31 (1), 44–72. doi:10.1002/hec.4524

Godman, B., Hill, A., Simoens, S., Selke, G., Selke Krulichova, I., Zampirolli Dias, C., et al. (2021). Potential approaches for the pricing of cancer medicines across Europe to enhance the sustainability of healthcare systems and the implications. *Expert Rev. Pharmacoecon Outcomes Res.* 21, 527–540. doi:10.1080/14737167.2021.1884546

Islam, F., Hain, D., Lewis, D., Law, R., Brown, L. C., Tanner, J. A., et al. (2022). Pharmacogenomics of clozapine-induced agranulocytosis: A systematic review and meta-analysis. *Pharmacogenomics J.* 22, 230–240. doi:10.1038/s41397-022-00281-9

Klarmann, H., Francis, J., and Rosenthal, G. (1968). Cost effectiveness analysis applied to the treatment of chronic renal disease. *Med. Care* 6, 48–54. doi:10.1097/00005650-196801000-00005

Luzzatto, L., Hyry, H. I., Schieppati, A., Costa, E., Simoens, S., Schaefer, F., et al. (2018). Outrageous prices of orphan drugs: A call for collaboration. *Lancet* 392, 791–794. doi:10.1016/S0140-6736(18)31069-9

Paoletti, X., Lewsley, L. A., Daniele, G., Cook, A., Yanaihara, N., Tinker, A., et al. (2020). Assessment of progression-free survival as a surrogate end point of overall survival in first-line treatment of ovarian cancer: A systematic review and meta-analysis. *JAMA Netw. Open* 3, e1918939. doi:10.1001/jamanetworkopen.2019.18939

Pontes, C., Zara, C., Torrent-Farnell, J., Obach, M., Nadal, C., Vella-Bonanno, P., et al. (2020). Time to review authorisation and funding for new cancer medicines in europe? Inferences from the case of olaratumab. *Appl. Health Econ. Health Policy* 18, 5–16. doi:10.1007/s40258-019-00527-x

Prasad, V., Kim, C., Burotto, M., and Vandross, A. (2015). The strength of association between surrogate end points and survival in oncology: A systematic review of trial-level meta-analyses. *JAMA Intern Med.* 175, 1389–1398. doi:10.1001/jamainternmed.2015.2829

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 28 June 2022
doi: 10.3389/fphar.2022.918493

Cost-Effectiveness of Pharmacogenomics-Guided Prescribing to Prevent Gene-Drug-Related Deaths: A Decision-Analytic Model

Cathelijne H. van der Wouden[1], *Heiralde Marck*[1], *Henk-Jan Guchelaar*[1], *Jesse J. Swen*[1] *and Wilbert B. van den Hout*[2]*

[1]Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, Netherlands

OPEN ACCESS

Edited by:
Antonio Javier Carcas Sansuán, Universidad Autónoma de Madrid, Spain

Reviewed by:
Abad Khan, University of Swabi, Pakistan
Francisco Abad-Santos, Universidad Autónoma de Madrid, Spain

***Correspondence:**
Wilbert B. van den Hout
W.B.van_den_Hout@lumc.nl

Specialty section:
This article was submitted to Pharmacogenetics and Pharmacogenomics, a section of the journal Frontiers in Pharmacology

Received: 12 April 2022
Accepted: 08 June 2022
Published: 28 June 2022

Citation:
van der Wouden CH, Marck H, Guchelaar H-J, Swen JJ and van den Hout WB (2022) Cost-Effectiveness of Pharmacogenomics-Guided Prescribing to Prevent Gene-Drug-Related Deaths: A Decision-Analytic Model. Front. Pharmacol. 13:918493. doi: 10.3389/fphar.2022.918493

Aim: Prospective studies support the clinical impact of pharmacogenomics (PGx)-guided prescribing to reduce severe and potentially fatal adverse effects. Drug-gene interactions (DGIs) preventing potential drug-related deaths have been categorized as "essential" by the Dutch Pharmacogenetics Working Group (DPWG). The collective clinical impact and cost-effectiveness of this sub-set is yet undetermined. Therefore, we aim to assess impact and cost-effectiveness of "essential" PGx tests for prevention of gene-drug-related deaths, when adopted nation-wide.

Methods: We used a decision-analytic model to quantify the number and cost per gene-drug-related death prevented, from a 1-year Dutch healthcare perspective. The modelled intervention is a single gene PGx-test for *CYP2C19, DPYD, TPMT or UGT1A1* to guide prescribing based on the DPWG recommendations among patients in the Netherlands initiating interacting drugs (clopidogrel, capecitabine, systemic fluorouracil, azathioprine, mercaptopurine, tioguanine or irinotecan).

Results: For 148,128 patients initiating one of seven drugs in a given year, costs for PGx-testing, interpretation, and drugs would increase by €21.4 million. Of these drug initiators, 35,762 (24.1%) would require an alternative dose or drug. PGx-guided prescribing would relatively reduce gene-drug related mortality by 10.6% (range per DGI: 8.1–14.5%) and prevent 419 (0.3% of initiators) deaths a year. Cost-effectiveness is estimated at €51,000 per prevented gene-drug-related death (range per DGI: €-752,000–€633,000).

Conclusion: Adoption of PGx-guided prescribing for "essential" DGIs potentially saves the lives of 0.3% of drug initiators, at reasonable costs.

Keywords: pharmacogenomics, cost-effectiveness, drug-related death, adverse drug reactions, precision medicine

1 INTRODUCTION

Pharmacogenomics (PGx)-guided prescribing promises to personalize drug therapy by using an individual's germline genetic makeup to guide dose and drug selection (Weinshilboum and Wang, 2004; Relling and Evans, 2015). This ameliorates the conventional 'trial and error' approach of drug prescribing, thereby reducing risk of lacking efficacy and adverse drug events (ADRs) (Pirmohamed, 2014). ADRs are a significant burden for individual patients and society and are an important cause of emergency department visits and hospital admissions (Leape et al., 1991; Lazarou et al., 1998; Pirmohamed et al., 2004). The resulting economic burden in the United States has been estimated at $30 billion to $136 billion annually (Johnson and Bootman, 1995). Several prospective studies support the clinical impact of individual gene-drug interactions (DGIs) to either optimize dosing (Pirmohamed et al., 2013; Verhoef et al., 2013; Coenen et al., 2015; Wu, 2015; Henricks et al., 2018) or drug selection (Mallal et al., 2008; Claassens et al., 2019a). Additionally, both the Clinical Pharmacogenetics Implementation Consortium (CPIC) (Relling and Klein, 2011; Relling et al., 2020) and the Dutch Pharmacogenetics Working Group (DPWG) (Swen et al., 2008; Swen et al., 2011; Swen et al., 2018) have developed guidelines on incorporating PGx results into drug prescribing. Appropriate sub-groups have previously been identified for PGx testing, including cardiovascular (Chatzopoulou et al., 2022) (supportive-) oncology (Patel, 2021; Patel et al., 2021), geriatric and polypharmacy patients (Brixner et al., 2016). Nevertheless, ambiguity remains regarding whether and which PGx tests should be prioritized for implementation into routine care (Roden et al., 2018). In an effort to overcome this inconclusiveness and to direct clinicians on requesting relevant PGx tests, the DPWG developed the Clinical Implication Score, where DGIs classified as "essential" direct clinicians to request a single-gene PGx test pre-therapeutically to guide dose and drug selection of the interacting drug (Swen et al., 2018). The Clinical Implication Score is based on the severity of clinical consequences associated with the DGI, the level of evidence for the association, the number needed to genotype to prevent an ADR with Common Terminology Criteria of Adverse Events (CTCAE) grade ≥3, and the level of PGx information included in the drug label. "Essential" DGIs comprise of high-risk drugs and corresponding recommendations intend to prevent severe clinical consequences such as gene-drug-related death. Therefore, they may be considered a minimum list of DGIs for which pre-therapeutic PGx-testing should be performed.

While numerous implementation barriers have been overcome, pre-therapeutic PGx-testing for all "essential" DGIs is not yet routine care and significant barriers preventing adoption remain (Swen et al., 2007; Haga and Burke, 2008; Abbasi, 2016). A prominent barrier is the lack of reimbursement of single-gene PGx tests, despite the availability of numerous cost-effectiveness analyses (Wong et al., 2010; Plumpton et al., 2016). Reimbursement of PGx tests for "essential" DGIs may be supported by studies quantifying the impact and cost-effectiveness of wide-spread adoption. Here, impact on the most severe outcome, mortality, may be most impactful.

Although the incidence of DGIs, when adopted nation-wide, has been estimated (Schildcrout et al., 2012; Samwald et al., 2016; Bank et al., 2019) and the cost-effectiveness of numerous DGIs in single-gene scenarios have been determined (Wong et al., 2010; Plumpton et al., 2016), the collective downstream effect of "essential" DGIs on clinical outcomes and cost-effectiveness after wide-spread adoption remains undetermined. Here, we therefore aim to assess the collective impact and cost-effectiveness of PGx for DGIs categorized as "essential" to prevent gene-drug-related deaths when adopted nation-wide in Netherlands using a decision-analytic model. The decision analytic model bases the risk of gene-drug-related death on literature review, the incidence of drug initiation on Dutch prescription data, and the predicted phenotype category frequencies on a Dutch sample.

2 METHODS

2.1 Study Design

We developed a decision-analytic model to assess the number and cost of gene-drug-related deaths prevented with PGx-guided initial dose and drug selection for "essential" DGIs, among patients initiating potentially interacting drugs in the Netherlands when compared to standard of care in 1 year. DGIs were selected based on the following criteria: 1) the clinical implication score is "essential", meaning that DPWG advises pre-therapeutic genotyping and 2) the DGI has clinical relevance score F (CTCAE Grade 5) and is therefore associated with gene-drug-related death for at least one predicted phenotype category. These selection criteria yielded the interactions between four genes (*CYP2C19, DPYD, TPMT*, and *UGT1A1*) and seven drugs (clopidogrel, capecitabine, systemic fluorouracil, azathioprine, mercaptopurine, tioguanine, and irinotecan). See **Table 1** for an overview of selected gene-drug pairs. When the DPWG recommendations suggested either dose reduction or an alternative drug, this model assumed dose reduction as the intervention.

2.2 Decision Analytic Model

The following model was used to calculate the number of gene-drug-related deaths prevented within 1 year:

$$N_{GDRDP} = \sum_{Drug=1}^{7} N_{Drug} \times \sum_{Pheno} P_{Pheno} \times \left(AR^{SoC}_{Drug,Pheno} - AR^{PGx}_{Drug,Pheno} \right)$$

N_{GDRDP} = gene-drug-related deaths prevented; N_{Drug} = number of drug initiators; P_{Pheno} = predicted phenotype

TABLE 1 | Selected "essential" gene-drug pairs, their potential consequences and DPWG recommendation per phenotype category.

Drug	Gene	Predicted phenotype	Actionable DGI	DPWG Recommendation	Most Severe Preventable Clinical Consequence Potentially Leading to Gene-Drug-Related death[a]
Azathioprine	*TPMT*	TPMT EM	No	-	-
		TPMT IM	Yes	Dose reduction to 50%	Severe myelosuppression
		TPMT PM	Yes	Dose reduction to 10% or alternative drug	Severe myelosuppression
Capecitabine	*DPYD*	DPYD GAS 0	Yes	Alternative drug	Fluoropyrimidine induced toxicity
		GAS 0.5/PHENO	Yes	Dose adjustment based on DPD phenotype	Fluoropyrimidine induced toxicity
		DPYD GAS 1.0	Yes	Dose reduction to 50%	Fluoropyrimidine induced toxicity
		DPYD GAS 1.5	Yes	Dose reduction to 50%	Fluoropyrimidine induced toxicity
		DPYD GAS 2.0	No	-	-
Clopidogrel	*CYP2C19*	CYP2C19 EM	No	-	-
		CYP2C19 IM	Yes	Dose increase to 200% or alternative drug	
		CYP2C19 PM	Yes	Alternative drug (ticagrelor, prasugrel or dipyridamole)	Cardiovascular death
		CYP2C19 UM	No	-	Cardiovascular death
Fluorouracil	*DPYD*	DPYD GAS 0	Yes	Alternative drug	Fluoropyrimidine induced toxicity
		GAS 0.5/PHENO	Yes	Dose adjustment based on DPD phenotype	Fluoropyrimidine induced toxicity
		DPYD GAS 1.0	Yes	Dose reduction to 50%	Fluoropyrimidine induced toxicity
		DPYD GAS 1.5	Yes	Dose reduction to 50%	Fluoropyrimidine induced toxicity
		DPYD GAS 2.0	No	-	-
Irinotecan	*UGT1A1*	UGT1A1[a]1/*1	No	-	-
		UGT1A1[a]1/*28	Yes	-	-
		UGT1A1[a]28/*28	Yes	Dose reduction to 70%	Severe myelosuppression and diarrhea
		UGT1A1 IM	No	-	-
		UGT1A1 PM	No	Dose reduction to 6%	Severe myelosuppression and diarrhea
Mercaptopurine	*TPMT*	TPMT EM	No	-	-
		TPMT IM	Yes	Dose reduction to 50%	Severe myelosuppression
		TPMT PM	Yes	Dose reduction to 10% or alternative drug	Severe myelosuppression
Tioguanine	*TPMT*	TPMT EM	No	-	-
		TPMT IM	Yes	Dose reduction to 50%	Severe myelosuppression
		TPMT PM	Yes	Dose reduction to 10% or alternative drug	Severe pancytopenia

[a]*Clinical relevance score: CTCAE, 5 (death), as reported in the summary of literature underlying the DPWG, recommendations; DGI, drug-gene interaction; EM, extensive metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; UM, ultra-rapid metabolizer; DPWG, dutch pharmacogenetics working group, and GAS = gene activity score.*

category; AR = absolute risk of gene-drug-related death within 1 year; SoC = for standard of care; PGx = for pharmacogenomics guided initial drug and dose selection.; Drug, Pheno = for a specific drug and a predicted phenotype category.

The following model was used to calculate the cost of gene-drug-related deaths prevented within 1 year:

$$Cost = \sum_{Drug=1}^{7} N_{Drug} \times \sum_{Pheno} P_{Pheno} \times \left(Cost_{PGx} + Cost_{HCP} + Cost^{PGx}_{Drug,Pheno} - Cost^{SoC}_{Drug,Pheno}\right)$$

N_{Drug} = number of drug initiators; P_{Pheno} = predicted phenotype category; $Cost_{PGx}$ = single-gene test; $Cost_{HCP}$ = physician and pharmacist time for interpretation and discussion of actionable PGx results; PGx = pharmacogenomics guided initial drug and dose selection; SoC = standard of care; Drug, Pheno = for a specific drug and a predicted phenotype category.

Finally, the cost per gene-drug-related death prevented was calculated by dividing cost by the number of deaths prevented both per individual DGI and overall.

2.3 Model Inputs

2.3.1 Number of Patients Initiating One of the Seven Drugs in the Netherlands

The number of patients a year initiating each of the seven drugs was estimated by multiplying the yearly number of users by the ratio of initiators and users. The yearly number of users was extracted from the Dutch nation-wide GIP databank from the most recent available year; azathioprine, clopidogrel, systemic fluorouracil and irinotecan from 2018, mercaptopurine and tioguanine from 2017 and capecitabine from 2014 (GIP Databank, 2021). For fluorouracil, only aggregated systemic

and cutaneous data are reported in the GIP databank. To exclude the cutaneous users we multiplied total number of users with the percentage of systemic fluorouracil users in the Leiden University Medical Center (LUMC) in 2018. The ratio of initiators and users was extracted per drug from the LUMC electronic medical record (EMR) for 2013 until 2018. Here users were defined as those who had a prescription for that drug in their EMR in this period and initiators were defined as users who lacked a prescription for that drug before 2018. See **Supplementary Table S1** for an overview of the used ratios and calculated number of nation-wide drug initiators.

2.3.2 Predicted Phenotype Category Frequencies

The predicted phenotype frequencies for the selected genes were derived from a Dutch sample (n = 1,023) (van der Wouden et al., 2019a). The variants tested to determine phenotype have been described in detail (van der Wouden et al., 2019a). The genotypes are translated into predicted phenotype categories based on functionalities as described in the DPWG recommendations (Swen et al., 2008; Swen et al., 2011; Swen et al., 2018).

2.3.3 Risk of Gene-Drug-Related Death

The most severe outcome among patients receiving standard of care, as reported in literature underlying the DPWG recommendations, associated with each "essential" DGI is shown in **Table 1**. Each DPWG recommendation suggests either a dose adjustment or selection of an alternative drug, to reduce the risk of both gene-drug-related deaths and other less severe ADRs. For our model, we extracted the absolute risk of gene-drug-related death within 1 year both in patients receiving the PGx-informed and standard of care (i.e., PGx uninformed) drug treatments for each predicted phenotype category independently, since the risk of gene-drug-related death varies across predicted phenotype categories. For example, the risk of fluoropyrimidine-induced toxicity increases with decreasing DPYD gene activity scores (GAS). Furthermore, when a PGx test is used to guide dose selection, individuals with an actionable phenotype (DPYD GAS 0–1.5) have a reduced risk of fluoropyrimidine-induced toxicity compared to individuals with an actionable phenotype using a normal dose. On the other hand, the risk of fluoropyrimidine-induced toxicity in individuals with a non-actionable predicted phenotype (DPYD GAS 2) will have the same mortality risk, regardless of being tested, since the dose is the same in both groups. Therefore, we have extracted the absolute risk of gene-drug-related death for each predicted phenotype category from the literature, across three groups: 1) tested-actionables (e.g., DPYD GAS 0, 0.5, 1 and 1.5 with PGx informed reduced dose), 2) non-actionables (e.g., DPYD GAS 2 with normal dose) and 3) untested-actionables (e.g., DPYD GAS 0, 0.5, 1 and 1.5 with normal dose). The actionable drug-gene pairs are categorized in **Table 1**.

A systematic methodology was used to select relevant publications from publications underlying the DPWG guideline which were suitable for risk extraction and is described in detail in **Supplementary Table S2**. In brief, six steps are performed chronologically until relevant publications have been selected from which absolute risk of gene-drug-related death for each of the tested and untested predicted phenotype categories can be extracted. The scientific rigor of publications decreases with each step and corresponds to the DPWG quality of evidence score (Swen et al., 2008; Swen et al., 2011). The first two steps select publications powered on mortality, the second two steps select publications powered on intermediate outcomes that are associated with mortality and the last two steps resort to additional literature search or estimation. Risk extraction is performed by using methodology corresponding to that step. Each extracted absolute risk of gene-drug-related death is given a certainty score based on the step in which publications are selected. The certainty score ranges from 4 (very certain) to 0 (very uncertain). An overall certainty score per DGI is calculated by taking the mean of the certainty scores of all tested and untested predicted phenotype categories. The systematic selection of publications and extracted absolute risks of gene-drug-related related deaths are described in **Supplementary Table S3**.

2.3.4 Predicted Phenotype Category Frequencies

The predicted phenotype frequencies for the selected genes were derived from a Dutch sample (n = 1,023). The variants tested to determine phenotype have been described in detail (van der Wouden et al., 2019b). The genotypes are translated into predicted phenotype categories based on functionalities as described in the DPWG recommendations.

2.3.5 Costs

Costs are estimated from a health care perspective, with a 1-year time-horizon, and are reported in Euros. The costs of different single-gene PGx tests were based on single-gene prices set in the LUMC in 2018 and on prices from the Dutch Healthcare Authority (NZa). This includes sample collection, analysis, and report of the predicted phenotype and dosing recommendation to the requesting pharmacist. The pharmacist time to record and discuss results with the physician and patient was set at 18 min. The physician time to discuss results with the pharmacist was set at 6 min. Time spent was multiplied by the hourly salaries of Clinical Pharmacists and Medical Specialists as standardized in Dutch Academic Hospitals in 2019 (Cao universitair medische centra, 2018-2020, 2020). The cost of drugs for both standard of care and PGx-guided treatments was calculated for a time-horizon of 1 year. The applied dose was based on the most common indication for the relevant drug and calculated using a base case of 75 kg and a body surface area of 1.7 m2. The price of drugs was extracted from the national drug price registry (Medicijnkosten.nl, 2021) by selecting the least expensive suitable dose and formulation. See **Supplementary Table S4** for an overview of the costs used in the model.

2.3.6 Model Assumptions

The adoption of PGx test requesting among initiators was assumed at 100%, DPWG recommendation adherence was

TABLE 2 | Overall Costs of PGx-testing, pharmacist and physician time for interpretation and drug treatment.

Drug	N drug Initiators	Cost of PGx Test/€ per Initiator	Average Cost of HCP Interpretation of Actionable PGx Result/€ per Initiator[a]	Average Cost of Drugs for Standard of Care (SoC) Treatment/€ per Initiator in 1 year	Average Cost of Drugs for PGx-Guided Treatment/€ per Initiator in 1 year	Difference in Average Drug Costs[b] (SoC-PGx) (% Saved)/€ per Initiator in 1 year	Total Costs for all initiators[c]/€
Azathioprine	6,979	132	1	248	237	11 (4.6%)	854,659
Capecitabine	8,860	132	1	1,204	1,158	46 (3.9%)	775,246
Clopidogrel	117,900	132	5	15	38	–24 (–62%)	18,923,430
Fluorouracil (systemic)	6,765	132	1	82	79	3 (4.0%)	880,112
Irinotecan	2,593	66	2	14,842	14,588	253 (1.7%)	-481,019
Mercaptopurine	2,177	132	1	1,956	1,875	81 (4.3%)	114,172
Tioguanine	2,854	132	1	1,088	1,080	7 (0.7%)	359,471
TOTAL for all initiators/€	148,128	19,381,790	586,167	60,519,056	61,977,169	–1,458,113	21,426,070
Mean per initiator/€	-	131	16[a]	409	418	10	145

PGx, pharmacogenomic.

[a]*Note: only those with an actionable drug-gene interaction will be interpreted by an HCP.*

[b]*[cost drugsstandard of care]-[cost drugsPGx-guided]*[Ndrug initiators].*

[c]*[costPGxtest]+[costpharmacist and physician time]-[costdrugs].*

assumed at 100% and the dose of drugs to be as per protocol for the indications which were investigated in publications from which risk data was extracted. Regarding the target population and allele frequencies, the ethnicity was assumed Caucasian, and patients were assumed to use similar comedications as patients enrolled in studies from which risks were extracted.

2.3.7 Funding and Ethical Approval

This study was funded by the European Community's Horizon 2020 Program under grant agreement No.668353 (U-PGx). The funder played no role in this study's design, conduct or report. Ethical approval was not required for this analysis. The data inputs are collected from publicly available sources.

3 RESULTS

As shown in **Table 2**, on a population of 17 million Dutch inhabitants, 148,128 patients initiate one of seven drugs in a given year, of which the clopidogrel initiators form the largest group (79.6%).

3.1 Impact on Costs

The total costs of single-gene PGx-testing, interpretation, and additional drugs would be €21.4 million (mean €145 per patient), of which the relevant single-gene test comprises 90.7% (€19.4 million in total, mean €131 per patient). Of these drug initiators, 35,762 (24.1%) would have an actionable DGI, requiring an alternative dose or drug. Health care professional (HCP) discussion of these actionable results would cost €586,000 (€16 per actionable patient). The extra drug costs made for initiating PGx-guided drug treatment is €1.5 million (€10 per patient), of which €2.4 million additional costs as a result of alternative drug treatment and €941,000 costs saved as a result of dose lowering. Interestingly, PGx-guided drug treatment costs are cost-saving for most DGIs (range per cost-saving DGI: 0.7–4.6%), except the clopidogrel-CYP2C19 interaction where the drug costs are €2.8 million higher (€24 per patient, +162%) than standard of care. For the irinotecan-UGT1A1 interaction, the costs of drugs saved in the PGx-guided group surmounts the cost of PGx-testing and HCP interpretation combined, making the intervention cost-saving with €481,000 on irinotecan drug costs.

3.2 Number of Gene-Drug-Related Deaths Prevented

As shown in **Table 3**, PGx-guided initial dose and drug selection would relatively reduce total gene-drug-related mortality by 10.6% (range per DGI: 8.1–14.5%) and prevent 419 (0.3% of initiators) deaths per year. The average certainty score was 2.5 (fairly certain) when weighed for deaths prevented or for number of patients, and ranged from of 0 (very uncertain) to 3 (certain) for individual DGIs.

3.3 Cost-Effectiveness Analysis

Preventing 419 gene-drug-related deaths with an increase of €21.4 million in healthcare costs, cost-effectiveness is estimated at €51,000 per prevented gene-drug-related death (range per DGI: €-752,000–€633,000). For the irinotecan-UGT1A1 interaction, PGx-guided treatment reduces both mortality and costs (resulting in a negative cost-effectiveness ratio).

4 DISCUSSION

Nation-wide adoption of PGx-guided initial dose and drug selection of "essential" DGIs can potentially save the lives of

TABLE 3 | Cost-effectiveness of PGx-guided pharmacotherapy for gene-drug interactions to prevent gene-drug-related deaths.

Drug	N drug Initiators	Predicted phenotype	Phenotype Frequency	N actionable DGI[a]	Absolute Risk Reduction/ % [b]	N gene-Drug-Related Deaths with Standard of Care	N gene-Drug-Related Deaths with PGx-Guided Care	N gene-Drug-Related Deaths prevented[c] (RRR%)	Number needed to genotype (NNG)[d]	Certainty Score	Cost to Prevent 1 GDR death[e]/€
Azathioprine	6,979	TPMT EM	0.912	0	0.00	15.8	13.5	2.3 (14.5%)	3,057	2 (fairly certain)	374,411
		TPMT IM	0.087	607	0.36						
		TPMT PM	0.001	7	0.97						
Capecitabine	8,860	DPYD GAS 0	0.001	9	0.76	22.4	20.6	1.8 (8.1%)	4,863	1 (uncertain)	425,488
		GAS 0.5/ PHENO	0.000	0	0.58						
		DPYD GAS 1.0	0.018	157	0.39						
		DPYD GAS 1.5	0.054	481	0.24						
		DPYD GAS 2.0	0.925	0	0.00						
Clopidogrel	117,900	CYP2C19 EM	0.673	0	0.00	3,887.8	3,477.0	410.8 (10.6%)	287	3 (certain)	46,064
		CYP2C19 IM	0.245	28,893	0.30						
		CYP2C19 PM	0.037	4,407	0.05						
		CYP2C19 UM	0.045	0	0.00						
Fluorouracil (systemic)	6,765	DPYD GAS 0	0.001	7	0.76	17.1	15.7	1.4 (8.1%)	4,863	1 (uncertain)	632,612
		GAS 0.5/ PHENO	0.000	0	0.58						
		DPYD GAS 1.0	0.018	120	0.39						
		DPYD GAS 1.5	0.054	367	0.24						
		DPYD GAS 2.0	0.925	0	0.00						
Irinotecan	2,593	UGT1A1 *1/*1	0.430	0	0.00	4.7	4.1	0.6 (13.6%)	4,055	2 (uncertain)	-752,191
		UGT1A1 *1/*28	0.466	0	0.00						
		UGT1A1 *28/*28	0.101	261	0.24						
		UGT1A1 IM	0.002	0	0.00						
		UGT1A1 PM	0.001	3	0.24						
Mercaptopurine	2,177	TPMT EM	0.912	0	0.00	4.9	4.2	0.7 (14.5%)	3,057	2 (fairly certain)	160,309
		TPMT IM	0.087	189	0.36						
		TPMT PM	0.001	2	0.97						
Tioguanine	2,854	TPMT EM	0.912	0	0.00	6.5	5.5	0.9 (14.5%)	3,057	0 (very uncertain)	385,084
		TPMT IM	0.087	248	0.36						
		TPMT PM	0.001	3	0.97						
TOTAL	148,128	-	-	35,762 (24.1%)	0.3	3,959	3,541	419 (10.6%)	-	2.5 (fairly certain)	51,187

DGI, drug-gene interaction; PGx-guided = pharmacogenomics guided; RRR, relative reduced risk; GDR, gene-drug-related death.

[a] *[Nactionable DGI]*[Pphenotype]*[Ndrug initiators].*

[b] *[absolute risk untestedphenotype]-[absolute risk testedphenotype].*

[c] *[N drug initiators]/[NNG].*

[d] *1/(SUMDGI [absolute risk reductionphenotype]*[P phenotype]).*

[e] *[total costs]/[Ndeaths prevented].*

419 (0.3% of drug initiators) a year at a cost of €51,000 per prevented death. The weighted average certainty score for this analysis 2.5 (fairly certain). In high-income countries an intervention is considered cost-effective when one gained quality-adjusted life year (QALY) costs less than a threshold between €20,000–60,000 (Nghiem et al., 2017). Since PGx-guided pharmacotherapy prevents gene-drug related deaths, it will contribute numerous QALYs; the magnitude of which is associated with the number of additional years that is gained by preventing the fatal gene-drug associated ADR. The investigated seven drugs are generally used to treat life-threatening diseases, and as a result, if treatment is effective and safe, patients will have a below-average though still considerable life-expectancy. Therefore, the additional cost of €51,000 per prevented death is well under the cost-effectiveness thresholds and can be considered reasonable and cost-effective.

4.1 Comparison to Current Literature

To our knowledge, we are the first to quantify both the collective impact and cost-effectiveness of nation-wide PGx-guided initial drug and dose selection for DGIs categorized as "essential" on mortality outcomes. Regarding collective impact, previous efforts have quantified the incidence of DGIs when adopted nation-wide (Schildcrout et al., 2012; Samwald et al., 2016; Bank et al., 2019). Bank et al. estimated that nation-wide adoption in the Netherlands of all DPWG recommendations would result in 23.6% of new prescriptions for PGx drugs would have an actionable DGI requiring adjustment of pharmacotherapy (Bank et al., 2019). However, the downstream impact on clinical outcomes were undetermined. In terms of cost-effectiveness, previous efforts have assessed individual drug-gene interactions but have not assessed the collective cost-effectiveness of "essential" DGIs. These include investigation of HLA-B*57:01 testing before abacavir initiation (Hughes et al., 2004), HLA-B*58:01 testing before allopurinol initiation (Plumpton et al., 2017), HLA-B*15:02 and HLA-A*31:01 before carbamazepine initiation and CYP2C9 and VKORC1 guided initial dosing of warfarin (Eckman et al., 2009). However, these DGIs were not considered "essential" by the DPWG and were therefore not included in our analysis. Consistent with individual DGIs investigated here, previous studies have shown the cost-effectiveness of UGT1A1 for irinotecan dosing (Gold et al., 2009; Butzke et al., 2016), CYP2C19 for clopidogrel dosing and alternative drug selection (Reese et al., 2012; Kazi et al., 2014), and TPMT guided initial dosing for thiopurines (Sluiter et al., 2019). Although a cost-minimization study for DPYD guided dosing has been performed (Henricks et al., 2019; Toffoli et al., 2019), its cost-effectiveness remains undetermined.

4.2 Model Design and Inputs

The outcome selected for this decision-analytic model is gene-drug-related death. This outcome excludes other, less severe, outcomes which may be improved by PGx-guided pharmacotherapy such as reduction in non-fatal ADRs or lack of drug efficacy. Excluding less severe but probably more prevalent gene-drug associated ADRs may therefore have resulted in an underestimation of the impact of PGx on patient outcomes. Taking these non-fatal ADRs into account would further confirm the cost-effectiveness of PGx-guided pharmacotherapy for "essential" DGIs. On the other side of the spectrum, while the PGx intervention decreases the risk of gene-drug associated ADRs, it may also increase risk of other negative effects such as loss of efficacy or increased risk for other ADRs. These are excluded from the current analysis and as a result we may have overestimated the (cost-)effectiveness. Regarding loss of efficacy, we expect equal drug exposures and benefit/risk among IMs and PMs receiving reduced doses and EMs receiving normal doses, as prospectively demonstrated (Henricks et al., 2018). The extent to which efficacy may be compromised is largest in drugs with a steep dose-response curve and where the default population dose is not at maximum effect or saturated receptor occupancy (Peck, 2018). Therefore, we do not expect that excluding loss of efficacy has affected our overall results much since efficacy was included in the intermediate outcome (which was a composite of death, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) for the most predominant DGI (clopidogrel-CYP2C19). The potential underestimation from excluding potential other ADRs can be illustrated by ADRs associated with the PGx-guided treatment. For example, although CYP2C19 guided treatment for clopidogrel dosing or alternative selection was non-inferior to treatment with ticagrelor or prasugrel at 12 months with respect to thrombotic events, treatment with ticagrelor or prasugrel resulted in higher incidence of minor bleeding (Claassens et al., 2019b). In this particular example, excluding minor bleeding from the mode has not affected the validity of our results, since minor bleeding do not result in drug-related death.

The time-horizon of the decision-analytic model was set at 1 year, consistent with the follow-up duration of the supporting trials. Ignoring impact beyond 1 year may have led to an underestimation of the benefit of the intervention. On the other hand, the imposed time-horizon overestimates the costs saved by the PGx intervention. In our current analysis we observed an overall cost increase for PGx-guided drug therapy when compared to standard of care which was driven by increased costs of PGx-guided alternatives for clopidogrel (increased cost of €2.8 million per year). Since clopidogrel is used life-long after a Transient Ischemic Attack, the additional drug costs will increase with an increasing time horizon. Additionally, we did not take into account potential dose or drug changes which may have occurred within standard of care, in the absence of a PGx test. If these changes were to be made within this 1 year time-horizon there would be no additional effect relative to the PGx intervention. This may be the case for drugs, such as fluoropyrimidines and thiopurines which may be dosed in standard of care upon other biomarkers, such as hematological counts.

Potential factors limiting the generalizability of the model are the underlying assumptions made. Firstly, to facilitate absolute risk extraction, we assumed each of the drug initiators to have one particular indication (as described in **Supplementary Table S3**) and to receive a corresponding standardized drug dose. However,

some drugs included in the analysis can be applied for numerous indications. Patients with these other indications may have a different baseline risk of gene-drug-related death as a result of variation in general health or clinical monitoring. Additionally, the effectiveness of PGx-guided prescribing may also vary across indications due to different applied doses. For example, we performed risk extraction for thiopurines on publications including Inflammatory Bowel Disease patients. However, a minority of patients initiating thiopurines has other indications such as Acute Lymphatic Leukemia or Rheumatoid Arthritis, which are applied at higher doses and among patients who are monitored more closely for myelosuppression. Therefore risk of drug-induced death may be different than those with Inflammatory Bowel Disease. Secondly, we assumed the ethnicity of the target population be Caucasian and therefore limited publication selection for absolute risk extraction to those performed in predominantly Caucasian samples. Since allele frequencies vary across ethnicities, we would be hesitant to extrapolate the reported results to ethnicities not included in the underlying publications. While for TMPT (McLeod et al., 1999) allele frequencies are fairly constant across ethnicities, the frequency of actionable phenotypes are higher for UGT1A1 in Blacks and Hispanics (Leger et al., 2018), CYP2C19 in Asians (Zhou et al., 2017) and DPYD in Africans (Mattison et al., 2006) and therefore the current analysis underestimates cost-effectiveness in these ethnicities. Thirdly, the current model was constructed for the Netherlands. Since the effectiveness of the PGx intervention may be dependent on the quality of the health-care system we would be hesitant to extrapolate our results to counties with a different quality of health-care system. If both the healthcare system and ethnicity is similar, we would suggest extrapolating our results to other countries in proportion to the population size (17 million).

In this study, we estimated the number of drug initiators of the investigated seven drugs to be 148,128 per year, with 24.1% of initiators having an actionable DGI. A previous study estimated the number of drug initiators for 45 drugs with a DPWG recommendation in the Netherlands to be much higher at 3,628,597 new prescriptions per year, with a similar portion of those with actionable DGI (23.6 vs. 24.1%) (Bank et al., 2019). This discrepancy is a result of the reported study using dispersion data from community pharmacies serving primary care. In contrast, our study used data encompassing primary and hospital care. Additionally, the previous study excluded drugs only applied in hospital care such as capecitabine, fluorouracil, and irinotecan. However, similar numbers of drug initiators are reported to be applied both in primary and hospital settings: azathioprine (6,943 vs. 6,979), clopidogrel (98,709 vs. 117,900), mercaptopurine (2,598 vs. 2,177) and thiopurine (1,883 vs. 2,854). Despite a seemingly large discrepancy initially, these numbers confirm the accuracy of the number of yearly drug initiators in the presented model.

In the presented analysis, we limited the input of costs to PGx-testing, HCP interpretation, and drugs and thereby we have excluded the cost of hospitalization as a result of gene-drug-related ADRs which do not lead to death. Despite this limited perspective, we argue that we have been conservative in estimation of costs. For example, the cost of PGx tests were based on 2018 LUMC prices, which are higher than the current prices in 2020. This confirms the prediction that costs of genetic tests are decreasing. Although performed with a different PGx intervention and target population, PGx cost-savings have previously been estimated at $218 per tested patient (Brixner et al., 2016). Additional cost-savings that were excluded are the reduced healthcare utilization resulting from reduced dose switching or reduced clinical monitoring (Toffoli et al., 2019). As a result, we are conservative in the cost of preventing gene-drug-related deaths and underestimate additional cost-saving.

4.3 Limitations

A key limitation of our approach is that the selected publications for risk of gene-related death extraction were powered on intermediate outcomes and not on drug-induced mortality (those corresponding to a certainty score 3 and lower). However, we do not expect PGx studies to be powered on mortality since these would require large sample sizes. As a result, we had to resort to the extraction of the absolute risk of intermediary outcomes, such as drug-induced myelosuppression, that are known to be associated with gene-drug-related death and multiplied this with the risk of mortality as a result of this intermediary outcome. While the extraction of the risk of mortality and intermediary outcomes was performed systematically based on literature underlying the DPWG, the risk of death as a result of intermediary outcomes was non-systematic, driven by the investigators' judgment of being suitable. Additionally, the majority of effect-sizes of PGx-guide prescribing to prevent gene-drug-related deaths are extracted from a number of observational studies. Ideally, these would be extracted from randomized controlled trials (RCTs) directly comparing PGx intervention to standard of care. However, we feel extraction from observational studies is substantiated since we do not expect RCTs to be performed for every individual DGI.

4.4 Future Research

The current study reports on seven "essential" DGIs in single-gene scenarios, but many more recommendations for actionable DGIs are available which intend to prevent non-fatal ADRs. From 2005 onwards the DPWG has developed 63 recommendations (Swen et al., 2008; Swen et al., 2011; Swen et al., 2018) and in parallel, the CPIC has devised 73 recommendations (Relling and Klein, 2011; Relling et al., 2020). In the near future, PGx delivery will shift from single-gene reactive model to a pre-emptive panel-testing model. Here, multiple pharmacogenes are tested simultaneously and recorded in the EMR in preparation of future prescriptions. Pre-emptive panel-testing may optimize both logistics and cost-effectiveness. This is supported by the observation that patients will receive multiple drug prescriptions with potential DGIs within their lifetime (Schildcrout et al., 2012; Samwald et al., 2016) and the fact that marginal acquisition costs of testing and interpreting additional pharmacogenes is near-zero (Roden et al., 2018).

However, the pre-emptive nature may also reduce cost-effectiveness, as not all tested individuals will actually benefit from the testing. Therefore, as implementation of PGx transitions from a single-gene approach to a pre-emptive panel approach, future efforts should quantify the cost-effectiveness of a panel of pharmacogenes to guide dose and drug selection of the remaining DGIs for which guidelines are available and over a longer time-horizon.

5 CONCLUSION

We used a decision-analytic model to assess the cost-effectiveness of nation-wide PGx-guided initial drug treatment for seven DGIs categorized as "essential" by the DPWG in the Netherlands. We found that nation-wide adoption of PGx-guided initial dose and drug selection of "essential" DGIs can potentially save the lives of 419 (0.3% of drug initiators) at reasonable costs (€51,000 per prevented death). The weighted average certainty score was 2.5 (fairly certain). These results support nation-wide adoption of PGx-guided initial drug treatment for "essential" DGIs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Cv–performed data collection, data analyses and prepared manuscript. HM–performed data collection, data analyses and prepared manuscript. JS–supervised data analyses and prepared manuscript. H-JG–supervised data analyses and prepared manuscript. Wv–supervised data analyses and prepared manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.918493/full#supplementary-material

REFERENCES

Abbasi, J. (2016). Getting Pharmacogenomics into the Clinic. *Jama* 316 (15), 1533–1535. doi:10.1001/jama.2016.12103

Bank, P. C. D., Swen, J. J., and Guchelaar, H. J. (2019). Estimated Nationwide Impact of Implementing a Preemptive Pharmacogenetic Panel Approach to Guide Drug Prescribing in Primary Care in The Netherlands. *BMC Med.* 17 (1), 110. doi:10.1186/s12916-019-1342-5

Brixner, D., Biltaji, E., Bress, A., Unni, S., Ye, X., Mamiya, T., et al. (2016). The Effect of Pharmacogenetic Profiling with a Clinical Decision Support Tool on Healthcare Resource Utilization and Estimated Costs in the Elderly Exposed to Polypharmacy. *J. Med. Econ.* 19 (3), 213–228. doi:10.3111/13696998.2015.1110160

Butzke, B., Oduncu, F. S., Severin, F., Pfeufer, A., Heinemann, V., Giessen-Jung, C., et al. (2016). The Cost-Effectiveness of UGT1A1 Genotyping before Colorectal Cancer Treatment with Irinotecan from the Perspective of the German Statutory Health Insurance. *Acta Oncol.* 55 (3), 318–328. doi:10.3109/0284186X.2015.1053983

Cao universitair medische centra 2018-2020 (2020). Voorwoord Van Cao-Partijen. Available from: https://www.nfu.nl/img/pdf/19.2084_Uitgave_2019_-_Cao_umc_NL_2018-2020_v8.pdf (Accessed November 2019).

Chatzopoulou, F., Kyritsis, K. A., Papagiannopoulos, C. I., Galatou, E., Mittas, N., Theodoroula, N. F., et al. (2022). Dissecting miRNA-Gene Networks to Map Clinical Utility Roads of Pharmacogenomics-Guided Therapeutic Decisions in Cardiovascular Precision Medicine. *Cells* 11 (4), 607. doi:10.3390/cells11040607

Claassens, D. M. F., Vos, G. J. A., Bergmeijer, T. O., Hermanides, R. S., van 't Hof, A. W. J., van der Harst, P., et al. (2019). A Genotype-Guided Strategy for Oral P2Y12 Inhibitors in Primary PCI. *N. Engl. J. Med.* 381 (17), 1621–1631. doi:10.1056/NEJMoa1907096

Claassens, D. M. F., Vos, G. J. A., Bergmeijer, T. O., Hermanides, R. S., van 't Hof, A. W. J., van der Harst, P., et al. (2019). A Genotype-Guided Strategy for Oral P2Y12 Inhibitors in Primary PCI. *N. Engl. J. Med.* 381 (17), 1621–1631. doi:10.1056/NEJMoa1907096

Coenen, M. J., de Jong, D. J., van Marrewijk, C. J., Derijks, L. J., Vermeulen, S. H., Wong, D. R., et al. (2015). Identification of Patients with Variants in TPMT and Dose Reduction Reduces Hematologic Events during Thiopurine Treatment of Inflammatory Bowel Disease. *Gastroenterology* 149 (4), 907–e7. e7. doi:10.1053/j.gastro.2015.06.002

Eckman, M. H., Rosand, J., Greenberg, S. M., and Gage, B. F. (2009). Cost-effectiveness of Using Pharmacogenetic Information in Warfarin Dosing for Patients with Nonvalvular Atrial Fibrillation. *Ann. Intern Med.* 150 (2), 73–83. doi:10.7326/0003-4819-150-2-200901200-00005

GIP Databank (2021). Open data farmacie en hulpmiddelen. Available from: https://www.gipdatabank.nl/servicepagina/open-data (Accessed November 2019).

Gold, H. T., Hall, M. J., Blinder, V., and Schackman, B. R. (2009). Cost Effectiveness of Pharmacogenetic Testing for Uridine Diphosphate Glucuronosyltransferase 1A1 before Irinotecan Administration for Metastatic Colorectal Cancer. *Cancer* 115 (17), 3858–3867. doi:10.1002/cncr.24428

Haga, S. B., and Burke, W. (2008). Pharmacogenetic Testing: Not as Simple as it Seems. *Genet. Med.* 10 (6), 391–395. doi:10.1097/GIM.0b013e31817701d4

Henricks, L. M., Lunenburg, C. A. T. C., de Man, F. M., Meulendijks, D., Frederix, G. W. J., Kienhuis, E., et al. (2019). A Cost Analysis of Upfront DPYD Genotype-Guided Dose Individualisation in Fluoropyrimidine-Based Anticancer Therapy. *Eur. J. Cancer* 107, 60–67. doi:10.1016/j.ejca.2018.11.010

Henricks, L. M., Lunenburg, C. A. T. C., de Man, F. M., Meulendijks, D., Frederix, G. W. J., Kienhuis, E., et al. (2018). DPYD Genotype-Guided Dose Individualisation of Fluoropyrimidine Therapy in Patients with Cancer: a Prospective Safety Analysis. *Lancet Oncol.* 19 (11), 1459–1467. doi:10.1016/S1470-2045(18)30686-7

Hughes, D. A., Vilar, F. J., Ward, C. C., Alfirevic, A., Park, B. K., and Pirmohamed, M. (2004). Cost-effectiveness Analysis of HLA B*5701 Genotyping in Preventing Abacavir Hypersensitivity. *Pharmacogenetics* 14 (6), 335–342. doi:10.1097/00008571-200406000-00002

Johnson, J. A., and Bootman, J. L. (1995). Drug-related Morbidity and Mortality. A Cost-Of-Illness Model. *Arch. Intern Med.* 155 (18), 1949–1956. doi:10.1001/archinte.155.18.1949

Kazi, D. S., Garber, A. M., Shah, R. U., Dudley, R. A., Mell, M. W., Rhee, C., et al. (2014). Cost-effectiveness of Genotype-Guided and Dual Antiplatelet Therapies in Acute Coronary Syndrome. *Ann. Intern Med.* 160 (4), 221–232. doi:10.7326/M13-1999

Lazarou, J., Pomeranz, B. H., and Corey, P. N. (1998). Incidence of Adverse Drug Reactions in Hospitalized Patients: a Meta-Analysis of Prospective Studies. *Jama* 279 (15), 1200–1205. doi:10.1001/jama.279.15.1200

Leape, L. L., Brennan, T. A., Laird, N., Lawthers, A. G., Localio, A. R., Barnes, B. A., et al. (1991). The Nature of Adverse Events in Hospitalized Patients. Results of the Harvard Medical Practice Study II. *N. Engl. J. Med.* 324 (6), 377–384. doi:10.1056/NEJM199102073240605

Leger, P., Chirwa, S., Nwogu, J. N., Turner, M., Richardson, D. M., Baker, P., et al. (2018). Race/ethnicity Difference in the Pharmacogenetics of Bilirubin-Related Atazanavir Discontinuation. *Pharmacogenet Genomics* 28 (1), 1–6. doi:10.1097/FPC.0000000000000316

Mallal, S., Phillips, E., Carosi, G., Molina, J. M., Workman, C., Tomazic, J., et al. (2008). HLA-B*5701 Screening for Hypersensitivity to Abacavir. *N. Engl. J. Med.* 358 (6), 568–579. doi:10.1056/NEJMoa0706135

Mattison, L. K., Fourie, J., Desmond, R. A., Modak, A., Saif, M. W., and Diasio, R. B. (2006). Increased Prevalence of Dihydropyrimidine Dehydrogenase Deficiency in African-Americans Compared with Caucasians. *Clin. Cancer. Res.* 12 (18), 5491–5495. doi:10.1158/1078-0432.CCR-06-0747

McLeod, H. L., Pritchard, S. C., Githang'a, J., Indalo, A., Ameyaw, M. M., Powrie, R. H., et al. (1999). Ethnic Differences in Thiopurine Methyltransferase Pharmacogenetics: Evidence for Allele Specificity in Caucasian and Kenyan Individuals. *Pharmacogenetics* 9 (6), 773–776. doi:10.1097/00008571-199912000-00012

Medicijnkosten.nl (2021). Vaak Bekeken. Available from: https://www.medicijnkosten.nl/ (Accessed November 2019).

Nghiem, S., Graves, N., Barnett, A., and Haden, C. (2017). Cost-effectiveness of National Health Insurance Programs in High-Income Countries: A Systematic Review. *PLoS One* 12 (12), e0189173. doi:10.1371/journal.pone.0189173

Patel, J. N., Arnall, J., Jandrisevits, E., Morse, A. L., Steuerwald, N., Copelan, E., et al. (2021). Pharmacogenomics-guided Supportive Oncology: A Tale of Two Trials. *Contemp. Clin. Trials* 105, 106391. doi:10.1016/j.cct.2021.106391

Patel, J. N. (2021). Opportunities for Pharmacogenomics-Guided Supportive Care in Cancer. *Support Care Cancer* 29 (2), 555–557. doi:10.1007/s00520-020-05892-1

Peck, R. W. (2018). Precision Medicine Is Not Just Genomics: The Right Dose for Every Patient. *Annu. Rev. Pharmacol. Toxicol.* 58, 105–122. doi:10.1146/annurev-pharmtox-010617-052446

Pirmohamed, M., Burnside, G., Eriksson, N., Jorgensen, A. L., Toh, C. H., Nicholson, T., et al. (2013). A Randomized Trial of Genotype-Guided Dosing of Warfarin. *N. Engl. J. Med.* 369 (24), 2294–2303. doi:10.1056/NEJMoa1311386

Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A. K., Walley, T. J., et al. (2004). Adverse Drug Reactions as Cause of Admission to Hospital: Prospective Analysis of 18 820 Patients. *BMJ* 329 (7456), 15–19. doi:10.1136/bmj.329.7456.15

Pirmohamed, M. (2014). Personalized Pharmacogenomics: Predicting Efficacy and Adverse Drug Reactions. *Annu. Rev. Genomics Hum. Genet.* 15, 349–370. doi:10.1146/annurev-genom-090413-025419

Plumpton, C. O., Alfirevic, A., Pirmohamed, M., and Hughes, D. A. (2017). Cost Effectiveness Analysis of HLA-B*58:01 Genotyping Prior to Initiation of Allopurinol for Gout. *Rheumatol. Oxf.* 56 (10), 1729–1739. doi:10.1093/rheumatology/kex253

Plumpton, C. O., Roberts, D., Pirmohamed, M., and Hughes, D. A. (2016). A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions. *PharmacoEconomics* 34 (8), 771–793. doi:10.1007/s40273-016-0397-9

Reese, E. S., Daniel Mullins, C., Beitelshees, A. L., and Onukwugha, E. (2012). Cost-effectiveness of Cytochrome P450 2C19 Genotype Screening for Selection of Antiplatelet Therapy with Clopidogrel or Prasugrel. *Pharmacotherapy* 32 (4), 323–332. doi:10.1002/j.1875-9114.2012.01048

Relling, M. V., and Evans, W. E. (2015). Pharmacogenomics in the Clinic. *Nature* 526 (7573), 343–350. doi:10.1038/nature15817

Relling, M. V., and Klein, T. E. (2011). CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. *Clin. Pharmacol. Ther.* 89 (3), 464–467. doi:10.1038/clpt.2010.279

Relling, M. V., Klein, T. E., Gammal, R. S., Whirl-Carrillo, M., Hoffman, J. M., and Caudle, K. E. (2020). The Clinical Pharmacogenetics Implementation Consortium: 10 Years Later. *Clin. Pharmacol. Ther.* 107 (1), 171–175. doi:10.1002/cpt.1651

Roden, D. M., Van Driest, S. L., Mosley, J. D., Wells, Q. S., Robinson, J. R., Denny, J. C., et al. (2018). Benefit of Preemptive Pharmacogenetic Information on Clinical Outcome. *Clin. Pharmacol. Ther.* 103 (5), 787–794. doi:10.1002/cpt.1035

Samwald, M., Xu, H., Blagec, K., Empey, P. E., Malone, D. C., Ahmed, S. M., et al. (2016). Incidence of Exposure of Patients in the United States to Multiple Drugs for Which Pharmacogenomic Guidelines Are Available. *PloS one* 11 (10), e0164972. doi:10.1371/journal.pone.0164972

Schildcrout, J. S., Denny, J. C., Bowton, E., Gregg, W., Pulley, J. M., Basford, M. A., et al. (2012). Optimizing Drug Outcomes through Pharmacogenetics: a Case for Preemptive Genotyping. *Clin. Pharmacol. Ther.* 92 (2), 235–242. doi:10.1038/clpt.2012.66

Sluiter, R. L., Van Marrewijk, C., De Jong, D., Scheffer, H., Guchelaar, H. J., Derijks, L., et al. (2019). Genotype-Guided Thiopurine Dosing Does Not Lead to Additional Costs in Patients with Inflammatory Bowel Disease. *J. Crohns Colitis* 13 (7), 838–845. doi:10.1093/ecco-jcc/jjz009

Swen, J. J., Huizinga, T. W., Gelderblom, H., de Vries, E. G., Assendelft, W. J., Kirchheiner, J., et al. (2007). Translating Pharmacogenomics: Challenges on the Road to the Clinic. *PLoS Med.* 4 (8), e209. doi:10.1371/journal.pmed.0040209

Swen, J. J., Nijenhuis, M., de Boer, A., Grandia, L., Maitland-van der Zee, A. H., Mulder, H., et al. (2011). Pharmacogenetics: from Bench to Byte-Aan Update of Guidelines. *Clin. Pharmacol. Ther.* 89 (5), 662–673. doi:10.1038/clpt.2011.34

Swen, J. J., Nijenhuis, M., van Rhenen, M., de Boer-Veger, N. J., Buunk, A. M., Houwink, E. J. F., et al. (2018). Pharmacogenetic Information in Clinical Guidelines: The European Perspective. *Clin. Pharmacol. Ther.* 103 (5), 795–801. doi:10.1002/cpt.1049

Swen, J. J., Wilting, I., de Goede, A. L., Grandia, L., Mulder, H., Touw, D. J., et al. (2008). Pharmacogenetics: from Bench to Byte. *Clin. Pharmacol. Ther.* 83 (5), 781–787. doi:10.1038/sj.clpt.6100507

Toffoli, G., Innocenti, F., Polesel, J., De Mattia, E., Sartor, F., Dalle Fratte, C., et al. (2019). The Genotype for DPYD Risk Variants in Patients with Colorectal Cancer and the Related Toxicity Management Costs in Clinical Practice. *Clin. Pharmacol. Ther.* 105 (4), 994–1002. doi:10.1002/cpt.1257

van der Wouden, C. H., van Rhenen, M. H., Jama, W. O. M., Ingelman-Sundberg, M., Lauschke, V. M., Konta, L., et al. (2019). Development of the PGx-Passport: A Panel of Actionable Germline Genetic Variants for Pre-emptive Pharmacogenetic Testing. *Clin. Pharmacol. Ther.* 106 (4), 866–873. doi:10.1002/cpt.1489

van der Wouden, C. H., van Rhenen, M. H., Jama, W. O. M., Ingelman-Sundberg, M., Lauschke, V. M., Konta, L., et al. (2019). Development of the PGx-Passport: A Panel of Actionable Germline Genetic Variants for Pre-emptive Pharmacogenetic Testing. *Clin. Pharmacol. Ther.* 106 (4), 866–873. doi:10.1002/cpt.1489

Verhoef, T. I., Ragia, G., de Boer, A., Barallon, R., Kolovou, G., Kolovou, V., et al. (2013). A Randomized Trial of Genotype-Guided Dosing of Acenocoumarol and Phenprocoumon. *N. Engl. J. Med.* 369 (24), 2304–2312. doi:10.1056/NEJMoa1311388

Weinshilboum, R., and Wang, L. (2004). Pharmacogenomics: Bench to Bedside. *Nat. Rev. Drug Discov.* 3 (9), 739–748. doi:10.1038/nrd1497

Wong, W. B., Carlson, J. J., Thariani, R., and Veenstra, D. L. (2010). Cost Effectiveness of Pharmacogenomics: a Critical and Systematic Review. *PharmacoEconomics* 28 (11), 1001–1013. doi:10.2165/11537410-000000000-00000

Wu, A. H. (2015). Pharmacogenomic Testing and Response to Warfarin. *Lancet* 385 (9984), 2231–2232. doi:10.1016/S0140-6736(14)62219-4

Zhou, Y., Ingelman-Sundberg, M., and Lauschke, V. M. (2017). Worldwide Distribution of Cytochrome P450 Alleles: A Meta-Analysis of Population-Scale Sequencing Projects. *Clin. Pharmacol. Ther.* 102 (4), 688–700. doi:10.1002/cpt.690

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

ORIGINAL RESEARCH
published: 19 July 2022
doi: 10.3389/fphar.2022.906956

Nivolumab Versus Sorafenib as First-Line Therapy for Advanced Hepatocellular Carcinoma: A Cost-Effectiveness Analysis

*Yan Li†, Xueyan Liang†, Huijuan Li, Tong Yang, Sitong Guo and Xiaoyu Chen**

Department of Pharmacy, Guangxi Academy of Medical Sciences and the People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, China

OPEN ACCESS

Edited by:
Isabelle Durand-Zaleski, Assistance Publique Hopitaux De Paris, France

Reviewed by:
Noa Gordon, Ben-Gurion University of the Negev, Israel
Fengyu Zhang, Global Clinical and Translational Research Institute, United States
Jonathan Salcedo, Analysis Group, United States

***Correspondence:**
Xiaoyu Chen
XiaoyuChen2010@outlook.com

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

Received: *29 March 2022*
Accepted: *20 June 2022*
Published: *19 July 2022*

Citation:
Li Y, Liang X, Li H, Yang T, Guo S and Chen X (2022) Nivolumab Versus Sorafenib as First-Line Therapy for Advanced Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. Front. Pharmacol. 13:906956. doi: 10.3389/fphar.2022.906956

Objective: Nivolumab improves overall survival (OS) and is associated with fewer adverse events than sorafenib for the treatment of advanced hepatocellular carcinoma (aHCC). However, the cost-effectiveness of nivolumab compared with sorafenib treatment for aHCC remains unclear. This study evaluated the cost-effectiveness of nivolumab and sorafenib in the treatment of aHCC.

Materials and methods: A partitioned survival model that included three mutually exclusive health states was used to evaluate the cost-effectiveness of nivolumab and sorafenib for treating aHCC. The clinical characteristics and outcomes of the patients in the model were obtained from the CheckMate 459. We performed deterministic one-way sensitivity and probabilistic sensitivity analyses to evaluate the robustness of the model. Subgroup analyses were also performed. Costs, life-years, quality-adjusted life-years (QALYs), incremental cost-effectiveness ratio (ICER), incremental net health benefits (INHB), and incremental net monetary benefits (INMB) were measured.

Results: The base case analysis showed that compared with sorafenib, treatment with nivolumab was associated with an increment of 0.50 (2.45 vs. 1.95) life-years and an increment of 0.32 (1.59 vs. 1.27) QALYs, as well as a $69,762 increase in cost per patient. The ICER was $220,864/QALY. The INHB and INMB were –0.15 QALYs and –$22,362 at a willingness-to-pay (WTP) threshold of $150,000/QALY, respectively. The probabilistic sensitivity analysis demonstrated that the probability of nivolumab being cost-effective was only 10.38% at a WTP threshold of $150,000/QALY. The model was most sensitive to the costs of sorafenib and nivolumab according to the one-way sensitivity analysis. When the price of sorafenib exceeded $0.93/mg or nivolumab was less than $24.23/mg, nivolumab was more cost-effective. The subgroup analysis illustrated that the probability of cost-effectiveness was >50% in the Barcelona Clinic Liver Cancer Stage B subgroups for nivolumab at a WTP threshold of $150,000/QALY. This study also showed that the probability of cost-effectiveness was <50% in most subgroups.

Conclusion: Nivolumab was not cost-effective, although it was associated with better clinical benefit and a favorable safety profile for the treatment of aHCC compared with sorafenib from the third-party payer perspective in the United States. If the price of

nivolumab is substantially reduced, favorable cost-effectiveness can be achieved among patients with aHCC.

Keywords: nivolumab, sorafenib, cost-effectiveness, advanced hepatocellular carcinoma, partitioned survival model

INTRODUCTION

Hepatocellular carcinoma (HCC) comprises 75–85% of primary liver cancer cases, and is the fourth-leading cause of annual cancer deaths worldwide (Gordan et al., 2020). Although diagnosis of HCC at early stages will possibly obtain curative treatments, such as resection or liver transplantation, only 30–40% of patients with HCC receive an early diagnosis (Forner et al., 2018). Most patients with HCC are diagnosed at an advanced stage and have a poor prognosis (Park et al., 2015). Therapies for advanced HCC (aHCC) include sorafenib (multikinase inhibitors) that increase median overall survival (OS) to 12.3 months (Kudo et al., 2018). However, sorafenib is associated with a high proportion of drug-related adverse events (AEs), and outcomes remain poor. Consequently, treatment options for aHCC remain very limited, and the prognosis is poor.

For the past few years, immunotherapy for many tumor types, including HCC, has received great attention (Zakeri et al., 2022). Nivolumab, an anti-programmed cell death protein-1 (PD-1) antibody, inhibits immune checkpoint signaling (Cheung et al., 2021). Nivolumab treatment for several tumor types, such as melanoma (Weber et al., 2015) and non-small cell lung cancer (Borghaei et al., 2015; Brahmer et al., 2015), improves survival compared with chemotherapy. The CheckMate-040 trial demonstrated the efficacy and safety of nivolumab as second-line therapy for aHCC (El-Khoueiry et al., 2017). With the increasing economic burden of healthcare costs, value-based oncology is drawing more attention; therefore, nivolumab has garnered great attention as a leading immunotherapy approach (Pei et al., 2021). Nivolumab has been approved in many countries for the treatment of sorafenib-receiving patients with aHCC, relying on the results of the CheckMate-040 trial (El-Khoueiry et al., 2017).

Recently, a CheckMate 459 phase 3 randomized multicenter clinical trial (Yau et al., 2022) reported the clinical activity and favorable safety of nivolumab as a first-line treatment for aHCC compared with sorafenib. The results revealed that the median follow-up for OS was 15.2 and 13.4 months for nivolumab and sorafenib treatment, respectively. In addition, the median OS was 16.4 and 14.7 months for nivolumab and sorafenib treatment, respectively. Although these increases were not statistically significant, they suggested that nivolumab might offer a potentially better survival chance. Moreover, the most common adverse event (AE) was palmar-plantar erythrodysesthesia, the incidence of which was lower following nivolumab treatment (<1%) than sorafenib treatment (14%). Thus, nivolumab may be a potential first-line alternative treatment for aHCC. However, with this convincing clinical outcome, the concomitant high drug price has been in the spotlight. To the best of our knowledge, no cost-effectiveness analyses comparing nivolumab with sorafenib for aHCC have been published. Cost-effectiveness analyses are helpful for optimally distributing limited healthcare resources to clinicians and decision-makers; it is necessary to perform a cost-effectiveness analysis to compare the efficacy and cost of nivolumab. Thus, from the third-party payer perspective in the United States (USA), this study evaluated the cost-effectiveness of nivolumab as a first-line therapy for aHCC.

MATERIALS AND METHODS

Patients and Intervention

This study was performed in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS, **Supplementary Table S1**) (Husereau et al., 2022). According to the People's Hospital of Guangxi Zhuang Autonomous Region, since publicly available data from the literature and open database were used to conduct this study rather than individual patient-level data, institutional review board review and informed consent were not required nor obtained.

Hypothetical target patients with aHCC were obtained from the CheckMate 459 randomized clinical trial (Yau et al., 2022). Included patients were adults (aged ≥18 years), with a performance status of 0 or 1 on the Eastern Cooperative Group scale; no previous systemic therapy; no previous radiotherapy within 4 weeks before study drug commencement; and had to have adequate hematological, hepatic, renal, and cardiac function. According to the CheckMate 459 trial report (Yau et al., 2022), patients assigned to the nivolumab group received 240 mg nivolumab intravenously every 2 weeks, and those in the sorafenib group received 400 mg of sorafenib orally twice daily. When the disease progressed or unacceptable AEs occurred, alternate therapies were administered.

Model Structure

In this study, we performed an economic evaluation and constructed a partitioned survival model based on three mutually exclusive health states: progression-free survival (PFS), progressive disease (PD), and death (**Figure 1**) (Williams et al., 2017). The time horizon was 10 years, and more than 98% patients died in both treatment arms. The cycle length was 1 week. In the model, the proportions of patients with OS and PFS were determined based on the results of the CheckMate 459 trial (Yau et al., 2022). The area under the OS curve was evaluated for the proportion of patients alive, the area under the PFS curve was evaluated for the proportion of patients alive with PFS, and the difference between the OS and PFS curves was evaluated for the proportion of patients alive with PD.

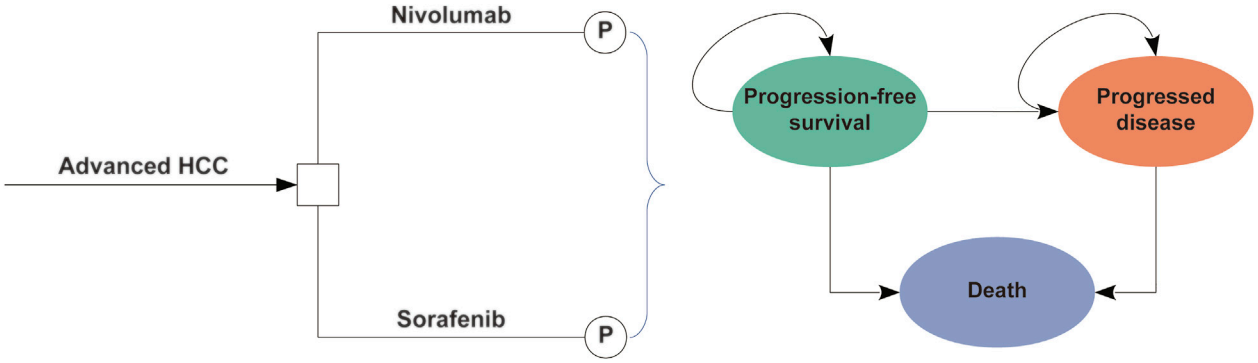

FIGURE 1 | The partitioned survival model consisting of three discrete health states. Abbreviations: HCC, hepatocellular carcinoma; P, partitioned survival model.

Clinical Data Inputs

The patients with aHCC in the nivolumab and sorafenib groups were determined based on the results of the CheckMate 459 trial (Yau et al., 2022). Both OS and PFS were extrapolated beyond the trial's follow-up time horizon that was calculated based on the algorithm created by Guyot et al. (2012). The Kaplan–Meier (K-M) survival curves of OS and PFS data were obtained from the trial using GetData Graph Digitizer version 2.26 (Get Data Graph Digitizer, 2022) to extract the individual patient data points. These data points were then used to fit the following parametric survival functions: exponential, Weibull, gamma, log-normal, Gompertz, log-logistic, and generalized gamma distributions. Subsequently, according to the value of Akaike information criterion (AIC) and Bayesian information criterion (BIC), the best-fit parametric models for the reconstructed K-M survival curves were selected. The results of the survival functions and parametric models of nivolumab and sorafenib treatment are shown in **Table 1**, and the goodness-of-fit results are shown in **Supplementary Table S2**. Log-normal was used to fit the OS and PFS K-M curves of nivolumab and sorafenib, respectively (**Supplementary Figure S1**). The key clinical input data are listed in **Table 1**.

Cost

Direct medical costs were evaluated, including the cost of acquiring drugs, attributed to the cost of the patient's health state, cost of supportive care, cost of terminal care, and AE-related costs (**Table 1**). The prices of acquiring drugs were collected from public databases (Centers for Medicare & Medicaid Services, 2022; RED BOOK online, 2022; Yau et al., 2022). The monitoring costs for patients with PFS and PD were $212 and $246 per cycle, respectively (Su et al., 2021). After the disease progression, about 57% of patients in the nivolumab group and 71% patients in the sorafenib group received second-line treatment according to published reports (Yau et al., 2022). The costs related to subsequent supportive care and terminal care were $39,875 and $8,488 per patient, respectively (Soto-Perez-de-Celis et al., 2019). The costs associated with severe adverse event (SAE, grade ≥3) management were sourced from the literature (**Supplementary Table S3**) (Patel et al., 2011; Barzey et al., 2013; Kacker et al., 2013; Hornberger et al., 2015; Wilson et al., 2017). All costs were adjusted to 2021 US dollars and were inflated to 2021 monetary values based on the Medical-Care Inflation data obtained from Tom's Inflation Calculator (Tom's Inflation Calculator, 2022), and these values are shown in **Table 1**.

Effectiveness

Health utility scores were assigned on a scale from 0 (death) to 1 (perfect health). Considering that health utilities for PFS and PD were not provided in CheckMate 459, we used health utility scores from the published literature (Shlomai et al., 2018). The utilities of PFS and PD related to aHCC were 0.76 and 0.68, respectively, which were obtained from an analysis of cost-effectiveness evaluating patients with HCC (Shlomai et al., 2018). The disutility values associated with AEs were also obtained from the literature (Amdahl et al., 2016).

Base Case Analysis

The incremental cost-effectiveness ratio (ICER), presented as the incremental cost per additional quality-adjusted life-years (QALYs) gained, was examined. Based on the published literature (Su et al., 2021), the WTP threshold in the United States was $150,000. When the ICER was lower than the WTP threshold ($150,000/QALY), cost-effectiveness was assumed according to the recommendations (Neumann et al., 2014). A 3% annual discount rate was derived for costs and utility outcomes (Sanders et al., 2016). We also calculated the incremental net health benefits (INHB) and incremental net monetary benefits (INMB) (Su et al., 2021). The INHB and INMB are computed according to the following formulas: $\mathrm{INHB}(\lambda) = (\mu_{E1} - \mu_{E0}) - (\mu_{C1} - \mu_{C0})/\lambda = \Delta E - \Delta C/\lambda$ and $\mathrm{INMB}(\lambda) = (\mu_{E1} - \mu_{E0}) \times \lambda - (\mu_{C1} - \mu_{C0}) = \Delta E \times \lambda - \Delta C$, where μ_{Ci} and μ_{Ei} were the cost and utility of nivolumab ($i = 1$) or sorafenib ($i = 0$), respectively, and λ was the WTP threshold.

Sensitivity Analyses

In this study, we performed one-way sensitivity analysis to identify significantly sensitive variables and evaluated the robustness of the results. One-way sensitivity analyses were performed based on different variables, such as costs and utilities, and the uncertainty of each variable was calculated

TABLE 1 | Key model inputs.

Parameter	Expected value (range)	Distribution	Source
Clinical input			
Survival model for sorafenib			
Log-normal model for PFS[a]	Log-mean = 2.98, log-SD = 0.88	ND	Yau et al. (2022)
Log-normal model for OS[a]	Log-mean = 4.07, log-SD = 1.13	ND	Yau et al. (2022)
Survival model for nivolumab[b]			
Log-normal model for PFS[a]	Log-mean = 3.05, log-SD = 1.10	ND	Yau et al. (2022)
Log-normal model for OS[a]	Log-mean = 4.23, log-SD = 1.30	ND	Yau et al. (2022)
HR for PFS associated with nivolumab vs. sorafenib	0.93 (0.79–1.10)	Log-normal: log-mean = −0.073, log-SD = 0.084	Yau et al. (2022)
HR for OS associated with nivolumab vs. sorafenib	0.85 (0.72–1.02)	Log-normal: log-mean = −0.16, log-SD = 0.089	Yau et al. (2022)
Utility input			
Utility of PFS	0.76 (0.57–0.95)	Beta: α = 4.7, β = 1.5	(Shlomai et al. (2018))
Utility of PD	0.68 (0.54–0.82)	Beta: α = 29, β = 13.6	(Shlomai et al. (2018))
Disutility due to AEs			
Grade 1 and 2	0.01 (0.008–0.012)	Beta: α = 18, β = 1283.2	(Amdahl et al. (2016))
Grade 3 and higher	0.16 (0.12–0.20)	Beta: α = 36, β = 193	(Amdahl et al. (2016))
Cost input			
Nivolumab per 200 mg[b]	5,849 (4,387–7,311)	Gamma: α = 53.41, β = 109.5	(Centers for Medicare & Medicaid Services, (2022); RED BOOK online, (2022))
Sorafenib per 200 mg[b]	158 (127–212)	Gamma: α = 39.09, β = 131.24	RED BOOK online, (2022)
Second-line treatment in nivolumab arm	5,131 (1,311–6,739)	Gamma: α = 53, β = 68.97	(Yau et al. (2022); Centers for Medicare & Medicaid Services, (2022); RED BOOK online, (2022))
Second-line treatment in sorafenib arm	3,656 (2,045–4,640)	Gamma: α = 99.88, β = 1.58	(Yau et al. (2022); Centers for Medicare & Medicaid Services, (2022); RED BOOK online, (2022))
Subsequent best supportive care per patient[c]	39,875 (29,906–49,843)	Gamma: α = 16, β = 2492.19	Soto-Perez-de-Celis et al. (2019)
Follow-up and monitoring per cycle			
Patients with PFS[d]	212 (159–265)	Gamma: α = 16, β = 13.25	(Su et al. (2021))
Patients with PD[d]	246 (185–308)	Gamma: α = 16, β = 15.38	(Su et al. (2021))
Drug administration per unit	80 (60–100)	Gamma: α = 16, β = 5	(Amdahl et al. (2016))
Terminal care per patient[d]	8,488 (6,366 to 10,610)	Gamma: α = 16, β = 530.5	(Soto-Perez-de-Celis et al. (2019))
Costs of AEs (more than grade 3)			
Nivolumab	503.94 (374.37–635.86)	Gamma: α = 53, β = 9.43)	(Patel et al. (2011); Barzey et al. (2013); Kacker et al. (2013); Wilson et al. (2017))
Sorafenib	3042.80 (2269.87–3822.95)	Gamma: α = 53, β = 56.97)	(Patel et al. (2011); Barzey et al. (2013); Kacker et al. (2013); Wilson et al. (2017))

Abbreviations: PFS, progression-free ; OS, overall survival; HR, hazard ratio; ND, not determined; PD, progressed disease; AEs, adverse events.

[a]*Only expected values are presented for these survival model parameters.*

[b]*Treatment with nivolumab and sorafenib continued until disease progression or unacceptable toxicity.*

[c]*Overall total cost per patient regardless of treatment duration.*

[d]*These costs were assumed to be continued until the health state transitioned.*

according to 95% confidence intervals (CIs) reported in the literature or estimated by assuming a 25% variation from the fundamental parameters (**Table 1**). We also conducted probabilistic sensitivity analysis with 10,000 iterations, for which Monte Carlo simulations were used. All parameters determined a suitable distribution (Vaidya et al., 2014). A gamma, log-normal, and beta distributions were assigned to the cost parameters, hazard ratios (HRs), and proportion, probability, and preference value parameters, respectively. Subsequently, a cost-effectiveness acceptability curve was constructed to illustrate the possibility that nivolumab or sorafenib would be valuable at various WTP levels/QALYs gain.

Subgroup Analyses

Subgroup analyses were performed to explore the uncertainty of the outcomes caused by different patient characteristics. Subgroup analyses were constructed for the different subgroups derived from CheckMate 459 by varying the HR for OS, including geographical region, age, Barcelona clinic liver cancer stage, Child–Pugh score, disease cause, vascular invasion or extrahepatic spread, baseline alpha-fetoprotein, and baseline tumor-cell PD-L1 expression (Yau et al., 2022). Statistical analyses in this study were performed with hesim and heemod packages in R, version 4.0.5, 2021 (R Foundation for Statistical Computing).

TABLE 2 | Summary of cost and outcome results in the base-case analysis.

Factor	Nivolumab	Sorafenib	Incremental change
Cost, $			
Drug[a]	366,661	299,477	67,184
Nondrug[b]	23,637	21,059	2,578
Overall	390,298	320,536	69,762
Life-years			
Progression-free	0.74	0.56	0.18
Overall	2.45	1.95	0.50
QALYs	1.59	1.27	0.32
ICER, $			
Per life-year	NA	NA	138,514
Per QALY	NA	NA	220,864
INHB, QALY, at threshold 150,000[a]	NA	NA	−0.15
INMB, $, at threshold 150,000[a]	NA	NA	−22,362

Abbreviations: ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; INMB, incremental net monetary benefit; NA, not applicable; QALYs, quality-adjusted life-years.

[a]Compared with sorafenib.

[b]Nondrug cost includes the costs of adverse event management, subsequent best supportive care per patient, and follow-up care covering physician monitors, drug administration, and terminal care.

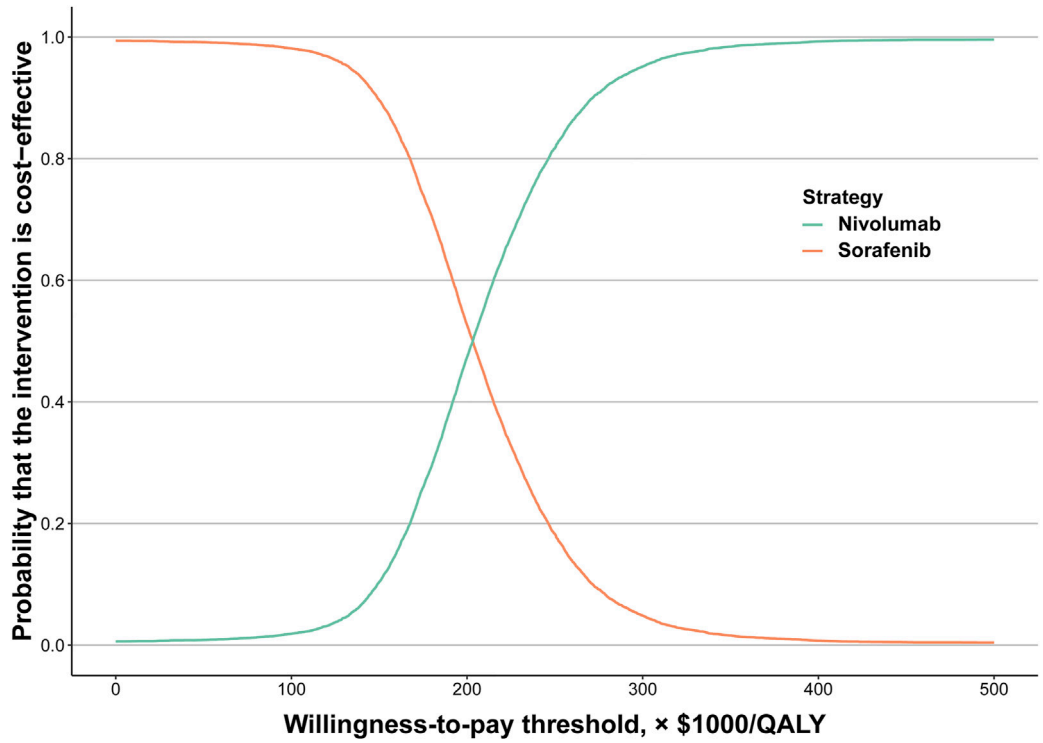

FIGURE 2 | Acceptability curves of cost-effectiveness for nivolumab versus sorafenib. Abbreviations: QALY, quality-adjusted life-year

RESULTS

Base Case Analysis

For base case analysis of the total patients with aHCC, nivolumab led to an increased effectiveness of 0.32 QALYs and 0.50 overall life-years, with an additional cost of $69,762 compared with the sorafenib arm. The corresponding ICER was $220,864/QALY. Furthermore, the INHB and INMB of nivolumab were −0.15 QALYs and −$22,362, respectively, at a $150,000/QALY WTP threshold compared with sorafenib (**Table 2**).

Sensitivity Analysis

The results of the one-way sensitivity analyses illustrated that the primary drivers of the model outcome included the cost of

TABLE 3 | Summary of subgroup analyses obtained by varying the hazard ratios (HRs) for overall survival.

Subgroup	Unstratified HR for OS (95% CI)	Change in cost, $[a]	Change in QALYs[a]	ICER, $/QALY	Cost-effectiveness probability of nivolumab, %, at threshold 150,000
Geographical region					
Asia	0.74 (0.56–0.98)	69,762	0.316	220,864	0.044
Non-Asia	0.92 (0.74–1.14)	22,805	0.123	185,040	0.44
Age, years					
<65	0.80 (0.63–1.02)	–71,081	–0.327	217,172	0.44
≥65	0.88 (0.68–1.12)	37,651	0.186	202,428	0.46
Barcelona Clinic Liver Cancer stage					
A	0.49 (0.17–1.40)	268,861	1.163	231,118	1.165
B	1.35 (0.86–2.11)	–83,919	–0.328	255,952	82.66
C	0.78 (0.65–0.95)	80,309	0.366	219,238	0.74
Child-Pugh score					
5	0.89 (0.72–1.10)	33,831	0.170	199,182	0.56
6	0.79 (0.57–1.09)	75,648	0.347	218,253	0.61
Disease cause					
Hepatitis C virus infected	0.71 (0.49–1.01)	115,754	0.516	224,272	0.87
Hepatitis B virus infected	0.77 (0.56–1.05)	85,065	0.386	220,140	0.51
Uninfected	0.95 (0.74–1.22)	12,396	0.079	156,425	0.61
Vascular invasion or extrahepatic spread					
Yes	0.74 (0.61–0.90)	-99,934	–0.449	222,440	0.65
No	1.14 (0.81–1.62)	41,657	0.149	279,143	49.76
Baseline alpha-fetoprotein, μg/L					
<400	0.98 (0.78–1.24)	2,562	0.038	67,990	0.5
≥400	0.67 (0.51–0.88)	138,456	0.612	226,201	1.1
Baseline tumor-cell PD-L1 expression					
≥1%	0.80 (0.54–1.19)	71,081	0.327	217,172	0.53
<1%	0.84 (0.69–1.02)	53,703	0.254	211,556	0.42

Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PD-L1, programmed cell death ligand 1; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

[a]HR for OS represents the HR of nivolumab vs. sorafenib for OS; change in cost and change in QALYs represent the results of nivolumab minus sorafenib.

sorafenib and nivolumab, as well as their utility for PD and PFS. This is because these factors have a considerable impact on the ICER (**Supplementary Figure S2**). The remaining parameters, such as HR for PFS and OS, were only moderately or weakly related to the outcomes and were not related to ICER exceeding the threshold of $150,000/QALY. We also evaluated the relevance of these key variables with the ICER between nivolumab and sorafenib. When the price of sorafenib exceeded $0.93/mg or nivolumab was less than $24.23/mg, nivolumab was cost-effective at a WTP threshold of $150,000/QALY (**Supplementary Figure S3**).

The results of the probabilistic sensitivity analysis were displayed by the cost-effectiveness acceptability curve (**Figure 2**). The probability of nivolumab being cost-effective increased as the WTP thresholds increased. Compared to sorafenib (89.62%), the probability of nivolumab being considered cost-effective was only 10.38% at a WTP threshold of $150,000/QALY for the total population. However, at a WTP threshold of $300,000/QALY, the probability of nivolumab and sorafenib being considered cost-effective was 95.14 and 4.86%, respectively.

Subgroup Analysis

The subgroup analysis was performed by varying the HRs for OS. Compared with sorafenib, nivolumab was associated with higher HRs in the subgroups of Barcelona clinic liver cancer stage B and without vascular invasion or extrahepatic spread [hazard ratio: 1.35 (95% CI: 0.86–2.11) and 1.14 (95% CI: 0.81–1.62), respectively]; hence, the results of subgroup analysis illustrated that nivolumab had >50% probability of being considered cost-effective in the Barcelona clinic liver cancer stage B subgroup at a WTP threshold of $150,000/QALY (**Table 3**). The probability of nivolumab being considered cost-effective was <50% in most of the subgroups.

DISCUSSION

In this study, we performed a cost-effectiveness analysis of nivolumab versus sorafenib for the therapy of aHCC, and the results of this study showed that compared with sorafenib, nivolumab was associated with incremental survival of 0.32 QALYs and incremental cost of $69,762 per patient. The calculated ICER was $220,864/QALY. One-way sensitivity analyses revealed that the cost of sorafenib and nivolumab was the most sensitive factor on the ICER, suggesting that the option between sorafenib and nivolumab could be made based on sorafenib and nivolumab costs. When the price of sorafenib exceeded $0.93/mg or nivolumab was less than $24.23/mg, nivolumab was cost-effective at a WTP threshold of $150,000/

QALY. In this study, nivolumab was unlikely to be a cost-effective option at a WTP threshold of $150,000/QALY compared with sorafenib for the therapy of aHCC. According to the results of comprehensive deterministic and probabilistic sensitivity analyses, the results of this model are robust. The cost-effectiveness acceptability curves revealed that the probability of nivolumab being cost-effective was 10.38% at the WTP threshold of $150,000/QALY.

The cost-effectiveness of the therapy is substantially affected by the WTP threshold. A total of $100,000 or $150,000/QALY has been recommended as the WTP threshold in the United States (Bae and Mullins, 2014; Neumann et al., 2014). The ICERs of cancer drugs are often higher than those of other drugs. Even so, the Food and Drug Administration still approves new drugs to treat tumors based on their effectiveness in the United States. Many new drugs are used to treat tumors, despite an ICER greater than $100,000 or $150,000/QALY. An ICER of $220,864/QALY for nivolumab was shown in this study compared with sorafenib, suggesting that the ICER was higher than the WTP thresholds of $150,000/QALY. This result does not suggest antithesis to the use of nivolumab among patients with aHCC, but rather suggests that policymakers can maximize health gains by spending more resources on more cost-effective interventions (Neumann et al., 2014).

Because the cost of immune checkpoint inhibitor development is high, their prices are often high (Siddiqui and Rajkumar, 2012). Thus, it is common to see that an immune checkpoint inhibitor is not cost-effective as mentioned in the published literature (Verma et al., 2018). A study compared the cost-effectiveness of nivolumab with docetaxel in recurrent metastatic head and neck squamous cell carcinoma (HNSCC); although nivolumab exhibits clinical benefit in HNSCC treatment, it is not cost-effective based on the list price (Zargar et al., 2018).

To the best of our knowledge, this study is the first to conduct cost-effectiveness analyses of nivolumab versus sorafenib as first-line treatment for aHCC. Previously, immune checkpoint inhibitors have been discussed for the treatment of other malignant neoplasms, such as lung cancer, head and neck cancers, renal cell cancer, and melanoma (Verma et al., 2018). The clinical importance of this study is worth discussing. If the government successfully negotiates with pharmaceutical companies, the price of the drug may be reduced so that nivolumab can be cost-effective (Siddiqui and Rajkumar, 2012). As shown in this study, at a WTP threshold of $150,000/QALY, when the cost of nivolumab was less than $24.23/mg or the cost of sorafenib exceeded $0.93/mg, nivolumab was cost-effective.

The advantages of this study are worth noting. First, to our knowledge, this is the first assessment to evaluate the cost-effectiveness of nivolumab for the treatment for aHCC by combining the latest randomized clinical trial with a partitioned survival model. Second, compared to sorafenib treatment, the price is favorable, and cost-effectiveness was also estimated for nivolumab treatment among patients with aHCC. Third, patients and physicians may benefit from the economic information of subgroups when tailoring treatment decisions.

There were some limitations to this analysis. First, health outcomes that exceeded the follow-up time of the CheckMate 459 trial were assumed by fitting parametric distributions to the reported K-M OS and PFS data, which may have resulted in uncertainty in the model outputs. This limitation may not be a major factor according to the sensitivity analysis results, indicating that this finding is generally robust. Second, the CheckMate 459 trial is a phase 3 randomized clinical trial, and the parameters in the model are based on its results. Thus, the cost and effectiveness of the results may have been affected by biases within the trial. For example, the patients with aHCC enrolled in the CheckMate 459 trial were generally healthier than the general population of patients with aHCC. In addition, compared to patients in real-world practice, those who participate in clinical trials generally have better adherence to treatment.

CONCLUSION

From the third-party payer perspective in the United States, this study suggests that at a WTP threshold of $150,000/QALY and under current drug pricing, nivolumab was unlikely to be considered cost-effective as first-line treatment for patients with aHCC compared with standard treatment with sorafenib. A substantial price reduction for nivolumab may result in favorable economic outcomes. Economic outcomes may be improved by tailoring individual treatments based on patient factors. These results may help clinicians to use appropriate treatments for patients with aHCC.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**; further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YL gathered and analyzed all data. Concept and design: YL, XL, and XC. Data interpretation: All authors. Drafting: YL and XL. Critical revision of the manuscript: All authors. Statistical analysis: YL and XL. Funding: XC. Technical and material support: HL, TY, and SG. Supervision: TY and SG.

FUNDING

This work was supported by the National Natural Science Foundation of China (No. 82160763).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.906956/full#supplementary-material

REFERENCES

Amdahl, J., Diaz, J., Park, J., Nakhaipour, H. R., and Delea, T. E. (2016). Cost-effectiveness of Pazopanib Compared with Sunitinib in Metastatic Renal Cell Carcinoma in Canada. *Curr. Oncol.* 23 (4), e340–54. doi:10.3747/co.23.2244

Bae, Y. H., and Mullins, C. D. (2014). Do value Thresholds for Oncology Drugs Differ from Nononcology Drugs? *J. Manag. Care Spec. Pharm.* 20 (11), 1086–1092. doi:10.18553/jmcp.2014.20.11.1086

Barzey, V., Atkins, M. B., Garrison, L. P., Asukai, Y., Kotapati, S., and Penrod, J. R. (2013). Ipilimumab in 2nd Line Treatment of Patients with Advanced Melanoma: a Cost-Effectiveness Analysis. *J. Med. Econ.* 16 (2), 202–212. doi:10.3111/13696998.2012.739226

Borghaei, H., Paz-Ares, L., Horn, L., Spigel, D. R., Steins, M., Ready, N. E., et al. (2015). Nivolumab versus Docetaxel in Advanced Nonsquamous Non-small-cell Lung Cancer. *N. Engl. J. Med.* 373 (17), 1627–1639. doi:10.1056/NEJMoa1507643

Brahmer, J., Reckamp, K. L., Baas, P., Crinò, L., Eberhardt, W. E., Poddubskaya, E., et al. (2015). Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-small-cell Lung Cancer. *N. Engl. J. Med.* 373 (2), 123–135. doi:10.1056/NEJMoa1504627

Centers for Medicare & Medicaid Services. (2022). ASP Drug Pricing Files. Available at: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2022-asp-drug-pricing-files, (Accessed 20 March 2022).

Cheung, K. S., Lam, L. K., Seto, W. K., and Leung, W. K. (2021). Use of Antibiotics during Immune Checkpoint Inhibitor Treatment Is Associated with Lower Survival in Hepatocellular Carcinoma. *Liver Cancer* 10 (6), 606–614. doi:10.1159/000518090

El-Khoueiry, A. B., Sangro, B., Yau, T., Crocenzi, T. S., Kudo, M., Hsu, C., et al. (2017). Nivolumab in Patients with Advanced Hepatocellular Carcinoma (CheckMate 040): an Open-Label, Non-comparative, Phase 1/2 Dose Escalation and Expansion Trial. *Lancet* 389 (10088), 2492–2502. doi:10.1016/s0140-6736(17)31046-2

Forner, A., Reig, M., and Bruix, J. (2018). Hepatocellular Carcinoma. *Lancet* 391 (10127), 1301–1314. doi:10.1016/s0140-6736(18)30010-2

GetData Graph Digitizer. (2022). Digitizing Software. Digitize Scanned Graphs and Get Original (X,y) Data. Available at: http://getdata-graph-digitizer.com, (Accessed 20 March 2022).

Gordan, J. D., Kennedy, E. B., Abou-Alfa, G. K., Beg, M. S., Brower, S. T., Gade, T. P., et al. (2020). Systemic Therapy for Advanced Hepatocellular Carcinoma: ASCO Guideline. *J. Clin. Oncol.* 38 (36), JCO2002672–4345. doi:10.1200/jco.20.02672

Guyot, P., Ades, A. E., Ouwens, M. J., and Welton, N. J. (2012). Enhanced Secondary Analysis of Survival Data: Reconstructing the Data from Published Kaplan-Meier Survival Curves. *BMC Med. Res. Methodol.* 12, 9. doi:10.1186/1471-2288-12-9

Hornberger, J., Hirsch, F. R., Li, Q., and Page, R. D. (2015). Outcome and Economic Implications of Proteomic Test-Guided Second- or Third-Line Treatment for Advanced Non-small Cell Lung Cancer: Extended Analysis of the PROSE Trial. *Lung Cancer* 88 (2), 223–230. doi:10.1016/j.lungcan.2015.03.006

Husereau, D., Drummond, M., Augustovski, F., de Bekker-Grob, E., Briggs, A. H., Carswell, C., et al. (2022). Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. *Bmj* 376, e067975. doi:10.1136/bmj-2021-067975

Kacker, S., Ness, P. M., Savage, W. J., Frick, K. D., McCullough, J., King, K. E., et al. (2013). The Cost-Effectiveness of Platelet Additive Solution to Prevent Allergic Transfusion Reactions. *Transfusion* 53 (11), 2609–2618. doi:10.1111/trf.12095

Kudo, M., Finn, R. S., Qin, S., Han, K. H., Ikeda, K., Piscaglia, F., et al. (2018). Lenvatinib versus Sorafenib in First-Line Treatment of Patients with Unresectable Hepatocellular Carcinoma: a Randomised Phase 3 Non-inferiority Trial. *Lancet* 391 (10126), 1163–1173. doi:10.1016/s0140-6736(18)30207-1

Neumann, P. J., Cohen, J. T., and Weinstein, M. C. (2014). Updating Cost-Effectiveness-Tthe Curious Resilience of the $50,000-Per-QALY Threshold. *N. Engl. J. Med.* 371 (9), 796–797. doi:10.1056/NEJMp1405158

Park, J. W., Chen, M., Colombo, M., Roberts, L. R., Schwartz, M., Chen, P. J., et al. (2015). Global Patterns of Hepatocellular Carcinoma Management from Diagnosis to Death: the BRIDGE Study. *Liver Int.* 35 (9), 2155–2166. doi:10.1111/liv.12818

Patel, D. A., Holdford, D. A., Edwards, E., and Carroll, N. V. (2011). Estimating the Economic Burden of Food-Induced Allergic Reactions and Anaphylaxis in the United States. *J. Allergy Clin. Immunol.* 128 (1), 110. doi:10.1016/j.jaci.2011.03.013

Pei, R., Shi, Y., Lv, S., Dai, T., Zhang, F., Liu, S., et al. (2021). Nivolumab vs Pembrolizumab for Treatment of US Patients with Platinum-Refractory Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma: A Network Meta-Analysis and Cost-Effectiveness Analysis. *JAMA Netw. Open* 4 (5), e218065. doi:10.1001/jamanetworkopen.2021.8065

RED BOOK online. (2022). IBM Micromedex; IBM Corporation. Available at: http://www.micromedexsolutions.com, (Accessed 20 March 2022).

Sanders, G. D., Neumann, P. J., Basu, A., Brock, D. W., Feeny, D., Krahn, M., et al. (2016). Recommendations for Conduct, Methodological Practices, and Reporting of Cost-Effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama* 316 (10), 1093–1103. doi:10.1001/jama.2016.12195

Shlomai, A., Leshno, M., and Goldstein, D. A. (2018). Regorafenib Treatment for Patients with Hepatocellular Carcinoma Who Progressed on Sorafenib-A Cost-Effectiveness Analysis. *PLoS One* 13 (11), e0207132. doi:10.1371/journal.pone.0207132

Siddiqui, M., and Rajkumar, S. V. (2012). The High Cost of Cancer Drugs and what We Can Do about it. *Mayo Clin. Proc.* 87 (10), 935–943. doi:10.1016/j.mayocp.2012.07.007

Soto-Perez-de-Celis, E., Aguiar, P. N., Cordón, M. L., Chavarri-Guerra, Y., and Lopes, G. L. (2019). Cost-Effectiveness of Cabozantinib in the Second-Line Treatment of Advanced Hepatocellular Carcinoma. *J. Natl. Compr. Canc Netw.* 17 (6), 669–675. doi:10.6004/jnccn.2018.7275

Su, D., Wu, B., and Shi, L. (2021). Cost-effectiveness of Atezolizumab Plus Bevacizumab vs Sorafenib as First-Line Treatment of Unresectable Hepatocellular Carcinoma. *JAMA Netw. Open* 4 (2), e210037. doi:10.1001/jamanetworkopen.2021.0037

Tom's Inflation Calculator. (2022). Medical-Care Inflation. Available at: https://www.halfhill.com/inflation_js.html, (Accessed 20 March 2022).

Vaidya, A., Severens, J. L., Bongaerts, B. W., Cleutjens, K. B., Nelemans, P. J., Hofstra, L., et al. (2014). High-sensitive Troponin T Assay for the Diagnosis of Acute Myocardial Infarction: an Economic Evaluation. *BMC Cardiovasc Disord.* 14, 77. doi:10.1186/1471-2261-14-77

Verma, V., Sprave, T., Haque, W., Simone, C. B., 2nd, Chang, J. Y., Welsh, J. W., et al. (2018). A Systematic Review of the Cost and Cost-Effectiveness Studies of Immune Checkpoint Inhibitors. *J. Immunother. Cancer* 6 (1), 128. doi:10.1186/s40425-018-0442-7

Weber, J. S., D'Angelo, S. P., Minor, D., Hodi, F. S., Gutzmer, R., Neyns, B., et al. (2015). Nivolumab versus Chemotherapy in Patients with Advanced Melanoma Who Progressed after Anti-CTLA-4 Treatment (CheckMate 037): a Randomised, Controlled, Open-Label, Phase 3 Trial. *Lancet Oncol.* 16 (4), 375–384. doi:10.1016/s1470-2045(15)70076-8

Williams, C., Lewsey, J. D., Mackay, D. F., and Briggs, A. H. (2017). Estimation of Survival Probabilities for Use in Cost-Effectiveness Analyses: A Comparison of a Multi-State Modeling Survival Analysis Approach with Partitioned Survival and Markov Decision-Analytic Modeling. *Med. Decis. Mak.* 37 (4), 427–439. doi:10.1177/0272989x16670617

Wilson, L., Huang, W., Chen, L., Ting, J., and Cao, V. (2017). Cost Effectiveness of Lenvatinib, Sorafenib and Placebo in Treatment of Radioiodine-Refractory Differentiated Thyroid Cancer. *Thyroid* 27 (8), 1043–1052. doi:10.1089/thy.2016.0572

Yau, T., Park, J. W., Finn, R. S., Cheng, A. L., Mathurin, P., Edeline, J., et al. (2022). Nivolumab versus Sorafenib in Advanced Hepatocellular Carcinoma (CheckMate 459): a Randomised, Multicentre, Open-Label,

Phase 3 Trial. *Lancet Oncol.* 23 (1), 77–90. doi:10.1016/s1470-2045(21)00604-5

Zakeri, N., Hall, A., Swadling, L., Pallett, L. J., Schmidt, N. M., Diniz, M. O., et al. (2022). Characterisation and Induction of Tissue-Resident Gamma Delta T-Cells to Target Hepatocellular Carcinoma. *Nat. Commun.* 13 (1), 1372. doi:10.1038/s41467-022-29012-1

Zargar, M., McFarlane, T., Chan, K. K. W., and Wong, W. W. L. (2018). Cost-Effectiveness of Nivolumab in Recurrent Metastatic Head and Neck Squamous Cell Carcinoma. *Oncologist* 23 (2), 225–233. doi:10.1634/theoncologist.2017-0277

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers | Frontiers in Pharmacology

TYPE Review
PUBLISHED 05 September 2022
DOI 10.3389/fphar.2022.919974

OPEN ACCESS

EDITED BY
Sheyu Li,
Sichuan University, China

REVIEWED BY
Si Wang,
Sichuan University, China
Wu Jun,
Jiujiang First People's Hospital, China

*CORRESPONDENCE
Audrey Huili Lim,
audreylim.moh@gmail.com

SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 19 April 2022
ACCEPTED 08 August 2022
PUBLISHED 05 September 2022

CITATION
Lim AH, Abdul Rahim N, Zhao J, Cheung SYA and Lin Y-W (2022), Cost effectiveness analyses of pharmacological treatments in heart failure .
Front. Pharmacol. 13:919974.
doi: 10.3389/fphar.2022.919974

Cost effectiveness analyses of pharmacological treatments in heart failure

Audrey Huili Lim[1]*, Nusaibah Abdul Rahim[2], Jinxin Zhao[3], S. Y. Amy Cheung[4] and Yu-Wei Lin[2,3]

[1]Institute for Clinical Research, National Institutes of Health, Shah Alam, Malaysia, [2]Malaya Translational and Clinical Pharmacometrics Group, Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy, University of Malaya, Kuala Lumpur, Malaysia, [3]Infection and Immunity Program and Department of Microbiology, Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia, [4]Certara (United States), Princeton, NJ, United States

In a rapidly growing and aging population, heart failure (HF) has become recognised as a public health concern that imposes high economic and societal costs worldwide. HF management stems from the use of highly cost-effective angiotensin converting enzyme inhibitors (ACEi) and β-blockers to the use of newer drugs such as sodium-glucose cotransporter-2 inhibitors (SGLT2i), ivabradine, and vericiguat. Modelling studies of pharmacological treatments that report on cost effectiveness in HF is important in order to guide clinical decision making. Multiple cost-effectiveness analysis of dapagliflozin for heart failure with reduced ejection fraction (HFrEF) suggests that it is not only cost-effective and has the potential to improve long-term clinical outcomes, but is also likely to meet conventional cost-effectiveness thresholds in many countries. Similar promising results have also been shown for vericiguat while a cost effectiveness analysis (CEA) of empagliflozin has shown cost effectiveness in HF patients with Type 2 diabetes. Despite the recent FDA approval of dapagliflozin and empagliflozin in HF, it might take time for these SGLT2i to be widely used in real-world practice. A recent economic evaluation of vericiguat found it to be cost effective at a higher cost per QALY threshold than SGLT2i. However, there is a lack of clinical or real-world data regarding whether vericiguat would be prescribed on top of newer treatments or in lieu of them. Sacubitril/valsartan has been commonly compared to enalapril in cost effectiveness analysis and has been found to be similar to that of SGLT2i but was not considered a cost-effective treatment for heart failure with reduced ejection fraction in Thailand and Singapore with the current economic evaluation evidences. In order for more precise analysis on cost effectiveness analysis, it is necessary to take into account the income level of various countries as it is certainly easier to allocate more financial resources for the intervention, with greater effectiveness, in high- and middle-income countries than in low-income countries. This review aims to evaluate evidence and cost effectiveness studies in more recent HF drugs i.e., SGLT2i, ARNi, ivabradine, vericiguat and omecamtiv, and gaps in current literature on pharmacoeconomic studies in HF.

KEYWORDS

heart failure, cost effectiveness analysis, pharmacoeconomics, SGLT 2 inhibitor, angiotensin receptor neprilysin inhibitor, ivabradine, vericiguat, omecamtiv

Introduction

Heart failure (HF) has become recognised as a public health concern that imposes high economic and societal costs worldwide (Di Tanna et al., 2019) as populations age and grow rapidly. HF management stems from the use of highly cost-effective angiotensin converting enzyme inhibitors (ACEi) and β-blockers (BB) to the use of newer drugs such as sodium-glucose cotransporter-2 inhibitors (SGLT2i), angiotensin receptor neprilysin inhibitor (ARNi), ivabradine, vericiguat, and omecamtiv.

Cost of HF management comprises of several components such as hospital management for acute decompensation, physician and outpatient visits, pharmacological management, and home care. However, devised based treatments for mechanical circulatory support, such as implantable cardioverter-defibrillators, as well as new and emerging pharmacological treatment and diagnostics tests have now led to significant increases in HF-related costs. Relatedly, this has placed a huge burden on healthcare systems, and widespread implementation of all potentially beneficial therapies for HF could prove unrealistic for many nations, especially in low- and middle-income countries (LMIC) (Rohde et al., 2013).

In light of recent additions to HF treatment options, it is imperative to understand the economic implications relative to cost effectiveness profiles of the respective pharmacological options. Modelling studies of pharmacological treatments that report on cost effectiveness in HF can help to quantify the relationship between clinical outcomes and help to guide clinical decision making (Rohde et al., 2013).

The objective of cost-effectiveness analysis is to determine if the value of an intervention justifies its cost. More specifically, cost-effectiveness analysis estimates the incremental cost required to improve a selected clinical outcome (e.g., cost per year of life saved, cost per stroke prevented) (Weinstein and Stason, 1977). In estimating the cost-effectiveness ratio, cost is typically measured in dollars. Health benefit, however, may be expressed in a variety of ways. To facilitate comparisons across diseases, health benefit is often quantified as the gain in quality-adjusted life years (QALYs). QALYs are designed to capture the effects of an intervention on both length and quality of life and are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale) (National Institute for Health and Care Excellence, 2022). Specifically, time spent in less-than-ideal health is adjusted downward where the degree of adjustment is determined by the utility for that health state e.g., the utility for an individual's present health state is 0.5 if the patient equates 2 years of life at their present health state with 1 year of life at ideal health (Rich and Nease, 1999).

In this article, we review evidence and cost effectiveness studies in more recent HF drugs i.e., SGLT2i, ARNi, ivabradine, vericiguat and omecamtiv, and gaps in current literature on pharmacoeconomic studies in HF.

Types of cost effectiveness analysis

Finite resource must be deployed effectively by policymakers in order for health progression while meeting new challenges and redressing inequities. This requires information on which interventions actually work, their cost, and experience with their implementation and delivery. Cost-effectiveness analysis is a way to examine both the costs and health outcomes of one or more interventions by comparing one intervention to another intervention (or the status quo) and approximating the costs required to gain a unit of a health outcome, e.g., a life year gained or a death prevented. Cost-effectiveness analysis helps identify ways to redirect resources to achieve more by demonstrating not only the utility of allocating resources from ineffective to effective interventions, but also the utility of allocating resources from less to more cost-effective interventions.

The decision tree

The simplest form of decision analysis models is the decision tree. Each mutually exclusive pathway begins with a "decision node" and goes through "chance nodes" to reach one of several "terminal nodes". Payoffs are defined at each "terminal node" i.e., costs of healthcare and/or QALY. Incremental cost-effectiveness ratio (ICER) can be estimated by comparing the costs and QALYs for each pathway and treatment option (Thomas and Chalkidou, 2016). Decision trees are most useful when health events are clustered together without repetition, when health events occur quickly or not at all, and when ambiguity of treatment effects are clarified rapidly. A major limitation of a decision tree is its unidirectional flow and as such, may be more suitable for acute disease where all relevant outcomes can be captured in a short time period (Edlin et al., 2015a).

The Markov model

The Markov model (named after the Russian mathematician Andrei Markov) is a stochastic process that undergoes transitions

TABLE 1 Types of cost effectiveness analyses and their advantages and disadvantages.

Type of cost effectiveness analysis	Advantages	Disadvantages
Decision tree	• Simple, easy to implement • Requires little data preparation • Able to handle both numerical and categorical data • Able to handle multi-output problems • Possible to validate a model using statistical tests • Performs well even if its assumptions are somewhat violated by the true model from which the data were generated	• Possible overfitting due to over-complex trees that do not generalise the data well • Not ideal for extrapolation as predictions of decision trees are neither smooth nor continuous, but piecewise constant approximations • Decision tree learners create biased trees if some classes dominate
Markov model	• Simplicity and out-of-sample forecasting accuracy • Generalisability • Based on a formal stochastic process, for which an analytical theory is available	• Inadequate in reflecting decision problems when complexity of decisions increases • Requires data normalisation
Micro-simulation	• Simulate the impact of interventions or policies on individual trajectories rather than the deterministic mean response of homogeneous cohorts • Individual-level simulation allows the inclusion of stochastic variation in disease progression as well as variation due to individual characteristics	• Statistically intensive • Increases likelihood of possible technical errors • Requires data normalisation

from one state to another (Li and Zhang, 2009). In the healthcare context, it assumes that patients move between mutually exclusive health states in cycles of a specified length, with death being an absorbing state, because once an individual has entered the state, they must remain there. The probability of a patient remaining in the initial state or moving on into one of the other health states is captured in the model where transitions occur within a defined time period, known as a "Markov cycle". In each model cycle, individuals have a certain probability of moving between health states, forwards and backwards. The length of model cycle can run for any period of time which allows for modelling up to a full lifetime of a patient (Edlin et al., 2015b; Graves et al., 2016; Komorowski and Raffa, 2016). In the case of heart failure, Markov models would be more ideal than decision trees. The main problem with Markov models is that they become very complicated when more states and more interactions between states are included, especially in the presence of time-dependent probabilities (Carta and Conversano, 2020).

Micro-simulation

Another decision analysis model is micro-simulation, an individual level state-transition model (Si et al., 2015). Micro-simulation models differ from decision tree or Markov frameworks by using individual level patient history to inform future risk; the other two models use cohort data and associate probability with the "average" patient (Briggs et al., 2006). Unfortunately, micro-simulations were rarely carried out in heart failure cost effectiveness analyses as most health utility estimates were derived from trial data (largely from the same trial for each particular drug). Further advantages and disadvantages of each type of analysis is shown in Table 1.

New drugs in heart failure and cost-effectiveness review

Cost-effectiveness analyses can help to quantify the relationship between clinical outcomes and the economic implications of new pharmacological treatments in HF. Gathering evidence from these modelling studies will assist in advising clinical decision making in pharmacological treatment, especially due to substantial increase in costs of HF management and widespread implementation of all potentially beneficial therapies for HF could prove unrealistic for many. Table 2 shows a summary of the cost effectiveness studies included in this review.

Sodium-glucose cotransporter-2 inhibitors

SGLT2i have recently risen in popularity in their use in HF. Several trials have been carried out to address this important knowledge gap, namely DAPA-HF, PRESERVED-HF, EMPA-REG OUTCOME, EMPEROR-Preserved, and SOLOIST-WHF.

TABLE 2 Summary of cost effectiveness studies included in review.

Drug	Study (first author, year)	Country	Time horizon	Comparator	ICER per QALY	Discount rate	Type of costs	Trial[a]	Type of HF
Dapagliflozin	Gil-Rojas et al. (2021)	Columbia[b]	5 years	SoC	USD$5,946	Cost: 5%; Eff: 5%	Drug acquisition, hospitalisation, emergency visit, adverse events, laboratory procedures	DAPA-HF	HFrEF
	Isaza et al. (2021)	United States	Lifetime	SoC	USD68,300	Cost: 3%; Eff: 3%	Drug acquisition, medications. urgent HF visits, hospitalization, background healthcare costs	DAPA-HF	HFrEF
	Jiang et al. (2021)	China[b]	10 years	SoC	USD$5,541.00	Cost: 5%; Eff: 5%	Drug acquisition, hospitalisation	DAPA-HF	HFrEF
	Krittayaphong and Permsuwan, (2021a)	Thailand[b]	Lifetime	SoC	USD$2,191 for non-diabetics; USD$1,527 for diabetics	Cost: 3%; Eff: 3%	Drug acquisition, medications. Hospitalization, adverse events	DAPA-HF	HFrEF
		Korea			USD$5,277	Cost: 3%	Drug acquisition, medications. Hospitalization		
		Australia			USD$9,980	Eff: 3%			
	Liao et al. (2021a)	Taiwan	15 years	SoC	USD$12,305			DAPA-HF	HFrEF
		Japan			USD$16,705				
		Singapore			USD$23,227				
		United Kingdom			£5,822	Cost: 3.5%; Eff: 3.5%	Drug acquisition, medications, hospitalization, patient review, blood chemistry checking, cardiologist visits, A&E referrals	DAPA-HF	HFrEF
	Mcewan et al. (2020)	Germany	Lifetime	SoC	€ 5,379	Cost: 3%; Eff: 3%		DAPA-HF	HFrEF
		Spain			€ 9,406	Cost: 3%; Eff: 3%		DAPA-HF	HFrEF
	Mendoza, 2021	Philippines[b]	Lifetime	SoC	USD$3,108 - 3,638	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation, adverse events	DAPA-HF	HFrEF
	Parizo et al. (2021)	United States	Lifetime	SoC	USD$83,650	Cost: 3%; Eff: 3%	Drug acquisition, medications, hospitalization, ambulatory care	DAPA-HF	HFrEF
	Yao et al. (2020)	China[b]	15 years	SoC	USD$3,827.6	Cost: 4.2%; Eff: 4.2%	Drug acquisition, medications, hospitalization	DAPA-HF	HFrEF
	Jiang et al. (2021)	China[b]	10 years	SoC	USD$6,946.69	Cost: 5%; Eff: 5%	Drug acquisition, hospitalisation	EMPEROR-Reduced	HFrEF
		Taiwan			USD$20,508	Cost: 3%	Drug acquisition, medications, hospitalization		
		Japan			USD$24,046	Eff: 3%			
Empagliflozin	Liao et al. (2021b)	South Korea	15 years	SoC	USD$8,846			EMPEROR-Reduced	HFrEF
		Singapore			USD$53,791				
		Thailand[b]			USD$21,543				
		Australia			USD$20,982				

(Continued on following page)

10.3389/fphar.2022.919974

TABLE 2 (*Continued*) Summary of cost effectiveness studies included in review.

Drug	Study (first author, year)	Country	Time horizon	Comparator	ICER per QALY	Discount rate	Type of costs	Trial[a]	Type of HF
	Reifsnider et al. (2020)	United Kingdom	10 years	SoC	£2,093	Cost: 3.5%; Eff: 3.5%	Drug acquisition, management of acute events, per-episode event costs	EMPA-REG-OUTCOME	HF in T2D
		United Kingdom			€ 20,400	Cost: 3.5%; Eff: 3.5%	Drug acquisition, hospitalisation, adverse events, background medical management, GP visits, outpatient contacts		
	Mcmurray et al. (2018)	Denmark	Lifetime	Enalapril	€ 22,600	Cost: 3%; Eff: 3%		PARADIGM-HF	HFrEF
		Columbia[b]			€ 11,200	Cost: 5%; Eff: 5%			
	Borges et al. (2020)	Portugal	30 years	Enalapril	€ 22,702	Cost: 5%; Eff: 5%	Drug acquisition, HF management, inpatient care, medical visits, adverse events	PARADIGM-HF	HFrEF
	Chin et al. (2020)	Australia	20 years	Enalapril	AUD$40,513	Cost: 5%; Eff: 5%	Drug acquisition, hospitalisation, death	PARADIGM-HF	HFrEF
	Gandjour and Ostwald, (2018)	Germany	Lifetime	Enalapril	€ 23,401	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation, general healthcare expenditure, laboratory monitoring	PARADIGM-HF	HFrEF
	Gaziano et al. (2020)	United States	Lifetime	Enalapril	USD$21,532	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation	PARADIGM-HF & PIONEER-HF	HFrEF hospitalisation
					USD$34,727 (*de novo* initiation)	Cost: 1.5%	Drug acquisition, hospitalisation, procedures		
	Grant, 2020	Canada	5 years	Enalapril	USD$40,234 (late initiation)	Eff: 1.5%		PARADIGM-HF	HFrEF
					USD$35,871 (early initiation)				
	King et al. (2016)	United States	Lifetime (40 years)	Enalapril	USD$50959	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation	PARADIGM-HF	HFrEF
	Krittayaphong and Permsuwan, (2018)	Thailand[b]	Lifetime	Enalapril	USD$4,857.11	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation	PARADIGM-HF	HFrEF
	Krittayaphong and Permsuwan (2021b)	Thailand[b]	Lifetime	Enalapril	USD$3,451.26	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation	PARADIGM-HF & PIONEER-HF	Acute decompensated HF
Sacubitril/ Valsartan	Liang et al. (2018)	Singapore	10 years	Enalapril	USD$55,198	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation, readmissions	PARADIGM-HF	HFrEF
	Park, 2019	South Korea	Lifetime	Enalapril	USD$11,970	Cost: 5%; Eff: 5%	Drug acquisition, hospitalisation, monitoring, adverse events, terminal care	PARADIGM-HF	HFrEF
	Perera et al. (2019)	Australia	Lifetime	Enalapril	AUD$77,889	Cost: 5%; Eff: 5%	Drug acquisition, hospitalisation, death	PIORNEER-HF	Acute decompensated HF

(Continued on following page)

10.3389/fphar.2022.919974

TABLE 2 (*Continued*) Summary of cost effectiveness studies included in review.

Drug	Study (first author, year)	Country	Time horizon	Comparator	ICER per QALY	Discount rate	Type of costs	Trial[a]	Type of HF
	Ramos, 2017	Netherlands	Lifetime	Enalapril	€ 17,600	Cost: 4%; Eff: 1.5%	Drug acquisition, HF management, hospitalisation, adverse events, informal care, traveling expenses	PARADIGM-HF	HFrEF
	Sandhu et al. (2016)	United States	Lifetime	Lisinopril	USD$44531 (NYHA Class II); USD$58194 (NYHA Class III)	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation, adverse events	PARADIGM-HF	HFrEF
	Van Der Pol et al. (2017)	Netherlands	30 years	Enalapril	€ 19,133	Cost: 4%; Eff: 1.5%	Drug acquisition, hospitalisation, elderly care and GP costs	PARADIGM-HF	HFrEF
	Wu et al. (2020)	China	10 years	Enalapril	USD$2,480.67	Cost: 3.5%; Eff: 3.5%	Drug acquisition, hospitalisation, outpatient visit, coay ratio for inpatient, cost of events, readmssion	PARADIGM-HF	HFrEF
	Zakiyah et al. (2021)	Indonesia[b]	10 years	Enalapril	USD$1,890	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation	PARADIGM-HF	HFrEF
	Zanfina, 2017	Switzerland	Lifetime	Enalapril	CHf25684	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation, management of HF by physicians, background drug therapy, adverse events, titration	PARADIGM-HF	HFrEF
	Zueger et al. (2018)	United States	5 years	Enalapril	USD$14,3891	Cost: 3%; Eff: 3%	Drug acquisition, hospitalisation	PARADIGM-HF	HFrEF
Ivabradine	Adena, 2018	Australia	10 years	SoC	AUD$14,905	Cost: 5%; Eff: 5%	Drug acquisition, medications. Hospitalization	SHIFT	Chronic HF
	Griffiths, 2014	United Kingdom	Lifetime	SoC	£8,498 for HR ≥75 bpm £13,764 for HR ≥ 70bpm	Cost: 3.5% Eff: 3.55%	Drug acquisition, hospitalization	SHIFT	Chronic HF
	Kansal, 2016	United States	10 years	SoC	USD$24,920	—	Drug acquisition, specialist visits, hospitalization, adverse events	SHIFT	Chronic HF
	Kourlaba, 2014	Greece	Lifetime	SoC	€ 9,986	Cost: 3.5%; Eff: 3.5%	Drug acquisition, hospitalisation, HF management	SHIFT	Chronic HF
	Krittayaphong et al. (2019)	Thailand[b]	Lifetime	SoC	USD$6,515	Cost: 3%; Eff: 3%	Drug acquisition, medications. hospitalization	SHIFT	HFrEF
	Taheri, 2018	Iran	10 years	SoC	USD$5,437	Cost: 7.2%; Eff: 5%	Drug acquisition, hospitalisation, medical care, HF management, adverse events	SHIFT	Chronic HF
Vericiguat	Alsumali, 2021	United States	30 years	SoC	USD$82,448	Cost: 3%; Eff: 3%	Drug acquisition, heart failure hospitalization, routine care, and terminal care	VICTORIA	HFrEF

[a]Name of trials included in this list in included in Supplementary Table S1.
[b]Low- or middle-income country.
Abbreviations: ICER, Incremental Cost Effectiveness Ratio; QALY, Quality Adjusted Life Years: SoC, Standard of Care; HFrEF, Heart Failure with Reduced Ejection Fraction; HF, Heart Failure; T2D, Type 2 Diabetes; Eff, Effect.

10.3389/fphar.2022.919974

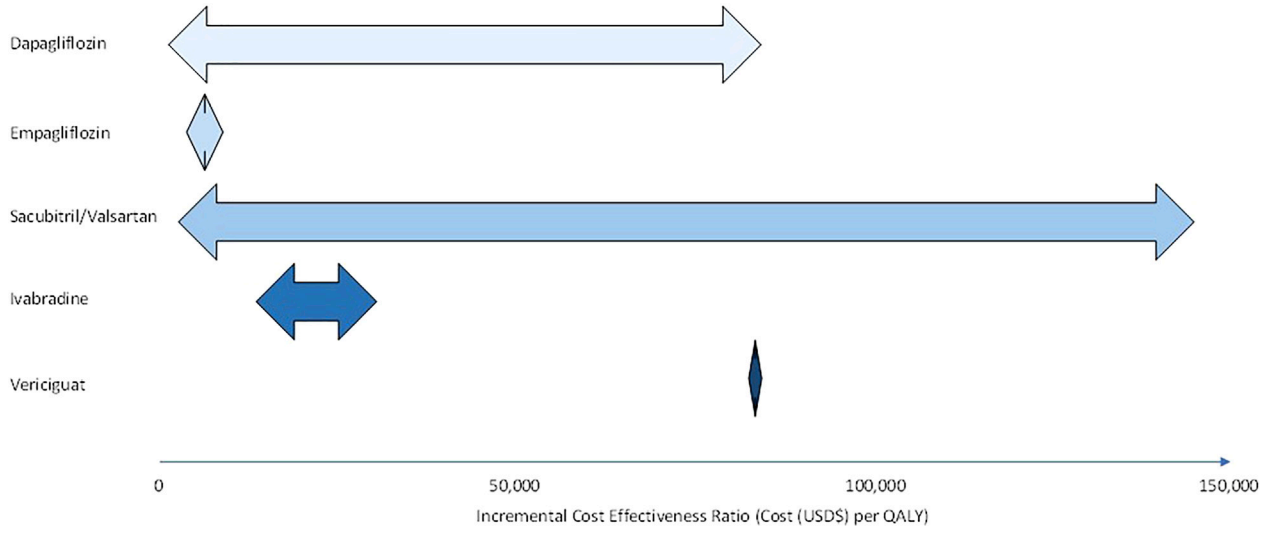

FIGURE 1
Range of incremental cost effectiveness ratios for dapagliflozin, empagliflozin, sacubitril/valsartan, ivabradine, and vericiguat in heart failure (HFrEF and HFpEF) patients.

Multiple systematic reviews and meta-analysis have shown that SGLT2i reduce all-cause and cardiovascular mortality in HFrEF across subgroups of sex, age, and race, regardless of baseline diabetes status (Zannad et al., 2020; Cardoso et al., 2021; Tsampasian et al., 2021).

Dapagliflozin was the first SGLT2i approved for the treatment of HFrEF. Results from DAPA-HF have been used in multiple cost effectiveness studies (Mcewan et al., 2020; Yao et al., 2020; Krittayaphong and Permsuwan, 2021a; Liao et al., 2021b; Gil-Rojas et al., 2021; Isaza et al., 2021; Jiang et al., 2021; Parizo et al., 2021), of which two were multinational health economic analysis. One was simulated in Germany, Spain and United Kingdom (Mcewan et al., 2020), the other in the Asia-Pacific region (Korea, Australia, Taiwan, Japan, and Singapore) (Liao et al., 2021b). The Kansas City Cardiomyopathy Questionnaire (KCCQ) total symptom score was used for quality of life measure in DAPA-HF. McEwan et al. reported treatment with dapagliflozin increased life-years and QALYs by 0.58 and 0.48 respectively, and reduced lifetime hospitalisations for HF by 105 events per 1,000 patients (Mcewan et al., 2020). The threshold for willingness-to-pay used was £20,000/QALY where more than 90% of simulations were cost-effective. Isaza et al. reported an ICER of $68,300/QALY in the United States of America (USA) (Isaza et al., 2021) but Krittayaphong and Permsuwan reported an ICER of $2,191/QALY in non-diabetics and $1,527/QALY in diabetics. This substantial difference highlights the importance of local settings when calculating cost effectiveness. ICERs based on United States settings have a tendency to be higher due to higher drug unit costs (Hewitt et al., 2018). A study from China showed that dapagliflozin had a lower ICER than empagliflozin when compared to standard treatment in HFrEF (Jiang et al., 2021), indicating dapagliflozin may be the preferred choice of SGLT2i in HFrEF.

Fewer cost effectiveness studies have been conducted on other SGLT2i (Reifsnider et al., 2020; Liao et al., 2021a). Reifsnider et al. showed that empagliflozin had an ICER of £2,093/QALY using data from HF subpopulation data from the EMPA-REG OUTCOME trial (Reifsnider et al., 2020). Liao et al. used transitional probabilities derived from the EMPEROR-Reduced trial to demonstrate ICER of $20,508, $24,046, $8,846, $53,791, $21,543, and $20,982 in Taiwan, Japan, South Korea, Singapore, Thailand, and Australia respectively (Liao et al., 2021a).

Despite mounting evidence of the use of SGLT2i in HFrEF, there has been a lack of evidence of its use in heart failure with preserved ejection fraction (HFpEF) which accounts for the majority of all HF in the community. The EMPEROR-Preserved trial was designed to address this knowledge gap, followed by the PRESERVED-HF, SOLOIST-WHF, SCORED, and DELIVER trials. With the exception of DELIVER (which is expected to be published in 2022), the other trials have delivered promising results of the use of SGLT2i in HFpEF (Bhatt et al., 2020a; Bhatt et al., 2020b; Anker et al., 2021; Nassif et al., 2021; Packer et al., 2021; Solomon et al., 2021). DELIVER was designed to complement DAPA-HF which assessed the efficacy of dapagliflozin in patients with HFrEF, specifically in patients with and without diabetes. The results of both studies will be pooled to assess the effects of dapagliflozin across the spectrum of

ejection fraction to allow for a wide range of patients with mildly reduced ejection fraction (Solomon et al., 2021).

Congestion and impaired renal function are hallmarks of all types of heart failure, including HFpEF, and appear to be ameliorated by SGLT2i. Therefore, SGLT2i may have beneficial effects across the range of LVEF by improving kidney function as chronic kidney disease is a major risk factor for adverse outcomes in HFpEF. SGLT2i also appear to improve diastolic function, reduce obesity, and visceral fat (including epicardial fat), reduce arterial stiffness, improve endothelial function, and reduce inflammation, all of which are important mechanisms of HFpEF pathogenesis (Solomon et al., 2021).

In line with recent NICE guidance (National Institute for Health and Care Excellence, 2021), the use of SGLT2i in the HFrEF population is beginning to increase. Hooper et al. (2021) found 85% of non-diabetic eligible patients were not treated with SGLT2i but predicted this figure is likely to fall significantly over the next year as awareness of this new treatment increases and local guidelines include this class of agent. Although the FDA has recently approved the use of empagliflozin in HFpEF, there is a lack of guideline-directed therapy for patients with HF with LVEF >40%.

Sacubitril/valsartan

Sacubitril/valsartan is the first angiotensin receptor neprilysin inhibitor (ARNi) for the treatment of HFrEF. PARADIGM-HF was a pivotal clinical trial that compared the effects of sacubitril/valsartan with enalapril and showed clinically relevant and statistically significant reduction in CV mortality and morbidity in patients with HFrEF (Krittayaphong and Permsuwan, 2018; Liu et al., 2021). This was followed by several smaller trials such as TITRATION, PRIME HF, EVALUATE-HF, PROVE-HF, PIONEER-HF, and TRANSITION. These trials highlight the range of use for sacubitril/valsartan, not only in chronic HF but also in the acute HF setting, suggesting the continuum of use across the outpatient and inpatient settings. However, CEAs have only been conducted in chronic HFrEF and acute decompensated HF.

PARADIGM-HF was a large, multicentre trial in the ambulatory setting while PIONEER-HF was designed specifically designed to assess outcomes in the acute in-hospital setting. This led to differing utility values from both trials and hence differing ICERs despite accounting for similar costs by Chin et al. (2020) and Perera et al. (2019). In this case, the studies by Perera et al. (2019), Gaziano et al. (2020), and Krittayaphong and Permsuwan (2021b) were the only ones which investigated acute decompensated HF, of which only the study from Thailand showed ICER below their local threshold.

A real-world effectiveness evaluation of sacubitril/valsartan by Proudfoot et al. (2021) indicated that most studies reported superior efficacy of sacubitril/valsartan in reducing the risk of HF hospitalisations, all-cause hospitalisations, and all-cause mortality as compared to standard of care. A significant improvement in NYHA functional class was observed, with studies reporting improvement in health-related quality of life (HRQoL). Although current guidelines for HF recommend ACEi/ARB as first line treatment, a systematic review by Tromp et al., 2022) has recently found that the combination of ARNi showed a smaller probability of all-cause mortality compared to ACEi/BB.

Despite regulatory approval in 2015, there has been poor uptake of sacubitril/valsartan for clinical use. As the drug acquisition cost of sacubitril/valsartan is higher than that of an ACEi, an estimation of expected costs and benefits is necessary for reimbursement by national payers in order to determine value for money. Various cost effectiveness analyses for sacubitril/valsartan in HF showed that the ICERs ranged from $1,890/QALY (Zakiyah et al., 2021) to $14,3891/QALY (Zueger et al., 2018). Although ICERs from most studies were below the implemented country-specific thresholds with the exception of Thailand and Singapore (King et al., 2016; Sandhu et al., 2016; Ademi et al., 2017; Van Der Pol et al., 2017; Gandjour and Ostwald, 2018; Krittayaphong and Permsuwan, 2018; Liang et al., 2018; Mcmurray et al., 2018; Zueger et al., 2018; Borges et al., 2020; Gaziano et al., 2020; Zakiyah et al., 2021), they were still less cost effective than dapagliflozin and empagliflozin. These studies used standard drug treatment of enalapril/lisinopril as comparators. With limited healthcare resources, compared with enalapril, sacubitril/valsartan may not be considered as a cost-effective strategy for chronic HF in Singaporean and Thai healthcare perspectives (Liu et al., 2021).

Ivabradine

Ivabradine is a selective I_f channel blocker that inhibits the pacemaker current of the sinoatrial node cells, which results in a reduced heart rate without affecting or lowering of blood pressure, or modification of cardiac contractility, or adverse modulating on the sympathetic system (Das et al., 2017; Badu-Boateng et al., 2018). The results from the SHIFT trial indicated that ivabradine therapy reduced CV death or hospitalisation, increased life expectancy and improved life quality in HFrEF. A range of economic evaluation studies of ivabradine simulated ICERs ranging from $10,616/QALY in Thailand (Krittayaphong et al., 2019) to $55,600/QALY in United States (Rashki Kemmak et al., 2021), indicating that ivabradine is more cost effective than sacubitril/valsartan but less than empagliflozin and dapagliflozin. In this case,

SGLT2i should be added on to HFrEF treatment before ivabradine.

Vericiguat

Vericiguat is a novel oral soluble guanylate cyclase stimulator which enhances the cyclic guanosine monophosphate (cGMP) pathway by directly stimulating soluble guanylate cyclase through a binding site independent of nitric oxide (Armstrong et al., 2020b; Lombardi et al., 2021). In the VICTORIA trial, patients with HFrEF were found to have lower CV death and hospitalisation. Cost effectiveness models based on data from this trial compared vericiguat to standard of care, leading to an ICER of $82,448/QALY. This placed vericiguat generally within the same cost effectiveness region as sacubitril/valsartan.

In patients with HFpEF, there have been contradicting evidence from two different trials, where vericiguat improved the pre-specified exploratory endpoint of KCCQ Clinical Summary Score by mean 19.3 points in the SOCRATES-PRESERVED (Pieske et al., 2017) but the VITALITY-HFpEF found that vericiguat did not improve the physical limitation score of the KCCQ (Armstrong et al., 2020a). Although some differences in characteristics of the study population may have led to this difference in findings and the lack of benefit with nitrates and phosphodiesterase inhibitors suggest that direct soluble guanylate cyclase stimulation with vericiguat is ineffective, further study in this area is warranted before excluding its use in HFpEF.

Omecamtiv

Omecamtiv mecarbil is a direct cardiac myosin activator currently being studied in the GALACTIC-HF trial. It increases systolic ejection time and stroke volume, improves ventricular remodelling, and decreases natriuretic peptide concentrations in patients with HFrEF. Post hoc analysis of results from the GALACTIC-HF trial showed that omecamtiv mecarbil may provide a clinically meaningful reduction in time to first HF event or CV death in patients with severe HF (Felker et al., 2022). Currently, there are plans for FDA approval of the drug in the coming year (Tilyou, 2021). Cost effectiveness analyses based on results from the GALACTIC-HF trial will be useful in order to quantify the benefit of omecamtiv mecarbil once it has received regulatory approval.

Gaps in studies and potential for future development

Of all the pharmacological treatment measures reviewed in this article, SGLT2i have the most extensive cost effectiveness analyses. Evaluation of the aforementioned cost effectiveness analyses shows that sacubitril/valsartan has the greatest range of ICERs (Figure 1). Baseline CV mortality risk score is the most commonly evaluated model drive in pharmacoeconomic evaluation of HF. It should be noted that there are few studies that evaluate treatment time horizon and hospitalisation costs. Furthermore, there is clearly a lack of studies that model rehospitalisation changes explicitly, only one study in this review included hospital readmissions in its cost evaluation (Wu et al., 2020). This is empirical in the case of HF as patients with HF who have previously been hospitalised have elevated rehospitalisation rates and increased care costs (Rohde et al., 2013).

Evaluation of the economic and societal implications of HF should take into account indicators of (re) hospitalisation which can provide crucial information beyond classification instruments and offer further details about patient profiles. However, one should be cautious with the use of generalised indicators for hospitalisation in a model structure due to potential for bias, as skewing in observations and related costs could occur in cases of multiple hospital visits (Di Tanna et al., 2019). The use of urgent heart failure visits as an endpoint could also be beneficial for modelling purposes as these visits which require intravenous diuretic therapy have been a component of the primary endpoint of several prior heart failure trials, including DAPA-HF, and have proven to be both prognostically similar to heart failure hospitalisations and similarly discriminative of treatment effects in several trials (Solomon et al., 2021).

Social perspectives as well as other costs can affect the cost effectiveness of various pharmacological treatment, especially if the drug of choice is costly, and these costs vary between countries. In evaluating cost effectiveness analyses, the threshold chosen by each country can have a significant impact on these results. Country income levels are likely to influence the ratio between the consumption value of health and threshold for health due to varying healthcare budgets. Limitations in increase of tax revenues are often a reason for constrained healthcare budgets (Woods et al., 2016), especially for LMICs. As drug costs differ in each country, the relative ratio of the new drug against the comparator tend to fluctuate. However, the disparity is more apparent in LMICs where low-cost generics of standard therapy (e.g., ACEi) are substantially cheaper that these newer drugs, and as such it may not be ideal to compare cost effectiveness analyses from high income countries to that of LMICs.

The disparity in choice of time horizons used in cost effectiveness studies reflects some variability in model structure. When simulated horizons are prolonged, respondent ICER tend to decrease (Yao et al., 2020). Variation in treatment time horizons affects the ICER as one that is too short may be unable to capture the benefit of the medication. For example, Zueger et al. (2018) showed an

ICER of USD$143891 for sacubitril/valsartan when compared with enalapril over 5 years while King et al. (2016) showed an ICER of USD50959 over a lifetime (approximated over 40 years). Similar costs were taken into account for both studies, the main difference was he length of the time horizon. This should also be taken into account when evaluating cost effectiveness analyses. Moreover, there has been a shift in trend away from cost-effectiveness analysis carried out using clinical trial data (or extrapolations from these) towards a modelling-based approach for example using Markov modelling. The use of a Markov model in this case is more ideal as heart failure has a continuous risk over time and has the possibility of more than one major event (e.g., (re) hospitalization, death). The use of deterministic sensitivity/scenario analysis and/or probabilistic sensitivity analysis is also essential to assess in detail the parameter uncertainty and the impact of key variables in the cost-effectiveness profiles.

One of the limitations of this review is we are unable to address the cost effectiveness of ivabradine, vericiguat, and omecamtiv appropriately due to the lack of studies on these newer drugs. As such, there is a need to address this gap in knowledge as well as looking into CEAs of sacubitril/valsartan in other conditions of HF aside from chronic HF and acute decompensated HF.

Furthermore, cost effectiveness studies that evaluate pharmacological therapy in HFpEF remains unexplored. As HF patients with less severe conditions and greater ejection fraction may obtain less benefit from add-on therapy, the cost-benefit ratio of using expensive pharmacological therapy may be smaller, hence greater ICER. As such, some drugs may only be cost effective in certain subgroups of patients.

HF treatment may also be guided by testing for B-type natriuretic peptide (BNP). BNP is a cardiac neurohormone secreted from the ventricles in response to ventricular volume expansion and pressure overload (Moe, 2006), whereby its increased presence in the blood is indicative of a higher risk of heart attack, heart failure or death (Lainchbury et al., 2009; Pfisterer et al., 2009; Porapakkham et al., 2010). Many clinical studies now recommend the use of BNP testing for diagnosing acute HF instead of the common and non-invasive method of echocardiography (Doust et al., 2006; Yoo, 2014). However, there is uncertainty about the cost effectiveness of BNP testing. A systematic review by Jafari et al. (2018) concluded that the use of BNP testing in patients with heart failure may reduce cost compared to the symptom-based clinical care and increase QALY. Treatment of HF should not only take into account cost of treatment but also possible testing for markers such as BNP which may improve cost effectiveness of treatment. However, it is to be noted that there has been a lack of cost effectiveness studies of BNP testing in LMICs, hence, an area to be further investigated.

Conclusion

In order for more precise analysis on cost effectiveness analyses, it is necessary to take into account the income level in various countries as it is certainly easier to allocate more financial resources for the intervention, with greater effectiveness, in high- and middle-income countries than in low-income countries. Although cost effectiveness analysis on newer pharmacological treatments such as SGLT2i, ARNi, ivabradine, vericiguat, and omecamtiv in HFrEF have been established, there is still a paucity of evidence for their use in HFpEF.

Author contributions

AL, NR, JZ, AC, and Y-WL conceptualised and designed the study. AL and Y-WL prepared the first draft of the manuscript, which was circulated for comments before further editing by NR, JZ, and SYC. All authors contributed to data interpretation, revised the draft critically for important intellectual content and agreed to the final submission.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.919974/full#supplementary-material

References

Ademi, Z., Pfeil, A. M., Hancock, E., Trueman, D., Haroun, R. H., Deschaseaux, C., et al. (2017). Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction. *Swiss Med. Wkly.* 147, w14533. doi:10.4414/smw.2017.14533

Anker, S. D., Butler, J., Filippatos, G., Ferreira, J. P., Bocchi, E., Böhm, M., et al. (2021). Empagliflozin in heart failure with a preserved ejection fraction. *N. Engl. J. Med.* 385, 1451–1461. doi:10.1056/NEJMoa2107038

Armstrong, P. W., Lam, C. S. P., Anstrom, K. J., Ezekowitz, J., Hernandez, A. F., O'connor, C. M., et al. (2020a). Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction: The VITALITY-HFpEF randomized clinical trial. *JAMA* 324, 1512–1521. doi:10.1001/jama.2020.15922

Armstrong, P. W., Pieske, B., Anstrom, K. J., Ezekowitz, J., Hernandez, A. F., Butler, J., et al. (2020b). Vericiguat in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* 382, 1883–1893. doi:10.1056/NEJMoa1915928

Badu-Boateng, C., Jennings, R., and Hammersley, D. (2018). The therapeutic role of ivabradine in heart failure. *Ther. Adv. Chronic Dis.* 9, 199–207. doi:10.1177/2040622318784556

Bhatt, D. L., Szarek, M., Pitt, B., Cannon, C. P., Leiter, L. A., Mcguire, D. K., et al. (2020a). Sotagliflozin in patients with diabetes and chronic kidney disease. *N. Engl. J. Med.* 384, 129–139. doi:10.1056/NEJMoa2030186

Bhatt, D. L., Szarek, M., Steg, P. G., Cannon, C. P., Leiter, L. A., Mcguire, D. K., et al. (2020b). Sotagliflozin in patients with diabetes and recent worsening heart failure. *N. Engl. J. Med.* 384, 117–128. doi:10.1056/NEJMoa2030183

Borges, M., Afonso-Silva, M., Laires, P. A., Gouveia, M., Alarcão, J., Ascenção, R., et al. (2020). Cost-effectiveness of sacubitril/valsartan for the treatment of patients with heart failure with reduced ejection fraction in Portugal. *Expert Rev. pharmacoecon. Outcomes Res.* 20, 199–205. doi:10.1080/14737167.2019.1628642

Briggs, A., Claxton, K., and Sculpher, M. (2006). Decision modelling for health economic evaluation. Oxford: Oxford University Press.

Cardoso, R., Graffunder, F. P., Ternes, C. M. P., Fernandes, A., Rocha, A. V., Fernandes, G., et al. (2021). SGLT2 inhibitors decrease cardiovascular death and heart failure hospitalizations in patients with heart failure: A systematic review and meta-analysis. *EClinicalMedicine* 36, 100933. doi:10.1016/j.eclinm.2021.100933

Carta, A., and Conversano, C. (2020). On the use of Markov models in pharmacoeconomics: Pros and cons and implications for policy makers. *Front. Public Health* 8, 569500. doi:10.3389/fpubh.2020.569500

Chin, K. L., Zomer, E., Wang, B. H., and Liew, D. (2020). Cost-effectiveness of switching patients with heart failure and reduced ejection fraction to sacubitril/valsartan: The Australian perspective. *Heart Lung Circ.* 29, 1310–1317. doi:10.1016/j.hlc.2019.03.007

Das, D., Savarese, G., Dahlström, U., Fu, M., Howlett, J., Ezekowitz, J. A., et al. (2017). Ivabradine in heart failure: The representativeness of SHIFT (systolic heart failure treatment with the IF inhibitor ivabradine trial) in a broad population of patients with chronic heart failure. *Circ. Heart Fail.* 10, e004112. doi:10.1161/CIRCHEARTFAILURE.117.004112

Di Tanna, G. L., Bychenkova, A., O'neill, F., Wirtz, H. S., Miller, P., Ó Hartaigh, B., et al. (2019). Evaluating cost-effectiveness models for pharmacologic interventions in adults with heart failure: A systematic literature review. *PharmacoEconomics* 37, 359–389. doi:10.1007/s40273-018-0755-x

Doust, J., Lehman, R., and Glasziou, P. (2006). The role of BNP testing in heart failure. *Am. Fam. Physician* 74, 1893–1898.

Edlin, R., Mccabe, C., Hulme, C., Hall, P., and Wright, J. (2015a). "Building a decision tree cost effectiveness model," in *Cost effectiveness modelling for health technology assessment: A practical course* (Cham: Springer International Publishing), 41–57.

Edlin, R., Mccabe, C., Hulme, C., Hall, P., and Wright, J. (2015b). "Introduction to Markov cost effectiveness models," in *Cost effectiveness modelling for health technology assessment: A practical course* (Cham: Springer International Publishing), 77–86.

Felker, G. M., Solomon, S. D., Claggett, B., Diaz, R., Mcmurray, J. J. V., Metra, M., et al. (2022). Assessment of omecamtiv mecarbil for the treatment of patients with severe heart failure: A post hoc analysis of data from the GALACTIC-HF randomized clinical trial. *JAMA Cardiol.* 7, 26–34. doi:10.1001/jamacardio.2021.4027

Gandjour, A., and Ostwald, D. A. (2018). Sacubitril/valsartan (LCZ696): A novel treatment for heart failure and its estimated cost effectiveness, budget impact, and disease burden reduction in Germany. *PharmacoEconomics* 36, 1285–1296. doi:10.1007/s40273-018-0688-4

Gaziano, T. A., Fonarow, G. C., Velazquez, E. J., Morrow, D. A., Braunwald, E., and Solomon, S. D. (2020). Cost-effectiveness of sacubitril-valsartan in hospitalized patients who have heart failure with reduced ejection fraction. *JAMA Cardiol.* 5, 1236–1244. doi:10.1001/jamacardio.2020.2822

Gil-Rojas, Y., Lasalvia, P., and García, Á. (2021). Cost-utility of dapagliflozin plus standard treatment compared to standard treatment for the management of heart failure with reduced ejection fraction in Colombia. *Expert Rev. Pharmacoeconomics Outcomes Res.* 22, 655–663. doi:10.1080/14737167.2022.1997595

Graves, N., Wloch, C., Wilson, J., Barnett, A., Sutton, A., Cooper, N., et al. (2016). A cost-effectiveness modelling study of strategies to reduce risk of infection following primary hip replacement based on a systematic review. *Health Technol. Assess.* 20, 1–144. doi:10.3310/hta20540

Hewitt, C., Foxon, G., Craddy, P., and Chunara, F. (2018). ICERS are not all the same. How cost-effectiveness estimates differ between the UK and US. *Value Health* 21, S30. doi:10.1016/j.jval.2018.04.189

Hooper, J., Shaw, S., Callan, P., and Williams, S. (2021). 150 SGLT2 inhibition in heart failure with a reduced ejection fraction: How many patients would benefit? *Heart* 107, A115.

Isaza, N., Calvachi, P., Raber, I., Liu, C.-L., Bellows, B. K., Hernandez, I., et al. (2021). Cost-effectiveness of dapagliflozin for the treatment of heart failure with reduced ejection fraction. *JAMA Netw. Open* 4, e2114501. doi:10.1001/jamanetworkopen.2021.14501

Jafari, A., Rezapour, A., and Hajahmadi, M. (2018). Cost-effectiveness of B-type natriuretic peptide-guided care in patients with heart failure: A systematic review. *Heart fail. Rev.* 23, 693–700. doi:10.1007/s10741-018-9710-3

Jiang, Y., Zheng, R., and Sang, H. (2021). Cost-effectiveness of adding SGLT2 inhibitors to standard treatment for heart failure with reduced ejection fraction patients in China. *Front. Pharmacol.* 12, 733681. doi:10.3389/fphar.2021.733681

King, J. B., Shah, R. U., Bress, A. P., Nelson, R. E., and Bellows, B. K. (2016). Cost-effectiveness of sacubitril-valsartan combination therapy compared with enalapril for the treatment of heart failure with reduced ejection fraction. *JACC. Heart Fail.* 4, 392–402. doi:10.1016/j.jchf.2016.02.007

Komorowski, M., and Raffa, J. (2016). "Markov models and cost effectiveness analysis: Applications in medical research," in *Secondary analysis of electronic health records* (Cham: Springer International Publishing), 351–367.

Krittayaphong, R., and Permsuwan, U. (2018). Cost-effectiveness analysis of sacubitril-valsartan compared with enalapril in patients with heart failure with reduced ejection fraction in Thailand. *Am. J. Cardiovasc. Drugs* 18, 405–413. doi:10.1007/s40256-018-0288-x

Krittayaphong, R., and Permsuwan, U. (2021a). Cost-utility analysis of add-on dapagliflozin treatment in heart failure with reduced ejection fraction. *Int. J. Cardiol.* 322, 183–190. doi:10.1016/j.ijcard.2020.08.017

Krittayaphong, R., and Permsuwan, U. (2021b). Cost-utility analysis of sacubitril-valsartan compared with enalapril treatment in patients with acute decompensated heart failure in Thailand. *Clin. Drug Investig.* 41, 907–915. doi:10.1007/s40261-021-01079-6

Krittayaphong, R., Yadee, J., and Permsuwan, U. (2019). Cost-effectiveness analysis of the adjunctive therapy of ivabradine for the treatment of heart failure with reduced ejection fraction. *Clin. Outcomes Res.* 11, 767–777. doi:10.2147/CEOR.S226568

Lainchbury, J. G., Troughton, R. W., Strangman, K. M., Frampton, C. M., Pilbrow, A., Yandle, T. G., et al. (2009). N-Terminal pro-B-type natriuretic peptide-guided treatment for chronic heart failure: Results from the BATTLESCARRED (NT-proBNP-Assisted treatment to lessen serial cardiac readmissions and death) trial. *J. Am. Coll. Cardiol.* 55, 53–60. doi:10.1016/j.jacc.2009.02.095

Li, W., and Zhang, C. (2009). "Markov chain analysis," in *International encyclopedia of human geography*. Editor A. Kobayashi. Second Edition (Oxford: Elsevier), 407–412.

Liang, L., Bin-Chia Wu, D., Aziz, M. I. A., Wong, R., Sim, D., Leong, K. T. G., et al. (2018). Cost-effectiveness of sacubitril/valsartan versus enalapril in patients with heart failure and reduced ejection fraction. *J. Med. Econ.* 21, 174–181. doi:10.1080/13696998.2017.1387119

Liao, C.-T., Yang, C.-T., Kuo, F.-H., Lee, M.-C., Chang, W.-T., Tang, H.-J., et al. (2021a). Cost-effectiveness evaluation of add-on empagliflozin in patients with heart failure and a reduced ejection fraction from the healthcare system's perspective in the asia-pacific region. *Front. Cardiovasc. Med.* 8, 750381. doi:10.3389/fcvm.2021.750381

Liao, C.-T., Yang, C.-T., Toh, H. S., Chang, W.-T., Chang, H.-Y., Kuo, F.-H., et al. (2021b). Cost-effectiveness evaluation of add-on dapagliflozin for heart failure with reduced ejection fraction from perspective of healthcare systems in Asia–Pacific region. *Cardiovasc. Diabetol.* 20, 204. doi:10.1186/s12933-021-01387-3

Liu, X. Q., He, L. S., Huang, J. Q., Xiong, L. J., Xia, C., and Lao, H. Y. (2021). Cost-effectiveness analyses of sacubitril-valsartan for heart failure. *Heart fail. Rev.* 26, 1119–1130. doi:10.1007/s10741-020-09956-6

Lombardi, C. M., Cimino, G., Pagnesi, M., Dell'aquila, A., Tomasoni, D., Ravera, A., et al. (2021). Vericiguat for heart failure with reduced ejection fraction. *Curr. Cardiol. Rep.* 23, 144. doi:10.1007/s11886-021-01580-6

Mcewan, P., Darlington, O., Mcmurray, J. J. V., Jhund, P. S., Docherty, K. F., Böhm, M., et al. (2020). Cost-effectiveness of dapagliflozin as a treatment for heart failure with reduced ejection fraction: A multinational health-economic analysis of DAPA-HF. *Eur. J. Heart Fail.* 22, 2147–2156. doi:10.1002/ejhf.1978

Mcmurray, J. J. V., Trueman, D., Hancock, E., Cowie, M. R., Briggs, A., Taylor, M., et al. (2018). Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. *Heart* 104, 1006–1013. doi:10.1136/heartjnl-2016-310661

Moe, G. W. (2006). B-type natriuretic peptide in heart failure. *Curr. Opin. Cardiol.* 21, 208–214. doi:10.1097/01.hco.0000221582.71619.84

Nassif, M. E., Windsor, S. L., Borlaug, B. A., Kitzman, D. W., Shah, S. J., Tang, F., et al. (2021). The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: A multicenter randomized trial. *Nat. Med.* 27, 1954–1960. doi:10.1038/s41591-021-01536-x

National Institute for Health and Care Excellence (2021). Dapagliflozin for treating chronic heart failure with reduced ejection fraction [Online]. London: National Institute for Health and Care Excellence ([Accessed March 1, 2022).

National Institute for Health and Care Excellence (2022). *Glossary* [online]. National Institute for health and care excellence. Available: https://www.nice.org.uk/glossary?letter=q#:~:text=One%20quality%2Dadjusted%20life%20year,a%200%20to%201%20scale (Accessed Feburary 16, 2022).

Packer, M., Butler, J., Zannad, F., Filippatos, G., Ferreira, J. P., Pocock, S. J., et al. (2021). Effect of empagliflozin on worsening heart failure events in patients with heart failure and preserved ejection fraction: EMPEROR-preserved trial. *Circulation* 144, 1284–1294. doi:10.1161/CIRCULATIONAHA.121.056824

Parizo, J. T., Goldhaber-Fiebert, J. D., Salomon, J. A., Khush, K. K., Spertus, J. A., Heidenreich, P. A., et al. (2021). Cost-effectiveness of dapagliflozin for treatment of patients with heart failure with reduced ejection fraction. *JAMA Cardiol.* 6, 926–935. doi:10.1001/jamacardio.2021.1437

Perera, K., Ademi, Z., Liew, D., and Zomer, E. (2019). Sacubitril-valsartan versus enalapril for acute decompensated heart failure: A cost-effectiveness analysis. *Eur. J. Prev. Cardiol.* 28, 966–972. doi:10.1177/2047487319878953

Pfisterer, M., Buser, P., Rickli, H., Gutmann, M., Erne, P., Rickenbacher, P., et al. (2009). BNP-Guided vs symptom-guided heart failure therapy: The trial of intensified vs standard medical therapy in elderly patients with congestive heart failure (TIME-CHF) randomized trial. *Jama* 301, 383–392. doi:10.1001/jama.2009.2

Pieske, B., Maggioni, A. P., Lam, C. S. P., Pieske-Kraigher, E., Filippatos, G., Butler, J., et al. (2017). Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: Results of the SOluble guanylate cyclase stimulatoR in heArT failurE patientS with PRESERVED EF (SOCRATES-PRESERVED) study. *Eur. Heart J.* 38, 1119–1127. doi:10.1093/eurheartj/ehw593

Porapakkham, P., Porapakkham, P., Zimmet, H., Billah, B., and Krum, H. (2010). B-Type natriuretic peptide-guided heart failure therapy: A meta-analysis. *Arch. Intern. Med.* 170, 507–514. doi:10.1001/archinternmed.2010.35

Proudfoot, C., Studer, R., Rajput, T., Jindal, R., Agrawal, R., Corda, S., et al. (2021). Real-world effectiveness and safety of sacubitril/valsartan in heart failure: A systematic review. *Int. J. Cardiol.* 331, 164–171. doi:10.1016/j.ijcard.2021.01.061

Rashki Kemmak, A., Dolatshahi, Z., Mezginejad, F., and Nargesi, S. (2021). Economic evaluation of ivabradine in treatment of patients with heart failure: A systematic review. *Expert Rev. Pharmacoecon Outcomes Res.*, 1–8.

Reifsnider, O. S., Kansal, A. R., Franke, J., Lee, J., George, J. T., Brueckmann, M., et al. (2020). Cost-effectiveness of empagliflozin in the UK in an EMPA-REG OUTCOME subgroup with type 2 diabetes and heart failure. *Esc. Heart Fail.* 7, 3910–3918. doi:10.1002/ehf2.12985

Rich, M. W., and Nease, R. F. (1999). Cost-effectiveness analysis in clinical practice: The case of heart failure. *Arch. Intern. Med.* 159, 1690–1700. doi:10.1001/archinte.159.15.1690

Rohde, L. E., Bertoldi, E. G., Goldraich, L., and Polanczyk, C. A. (2013). Cost-effectiveness of heart failure therapies. *Nat. Rev. Cardiol.* 10, 338–354. doi:10.1038/nrcardio.2013.60

Sandhu, A. T., Ollendorf, D. A., Chapman, R. H., Pearson, S. D., and Heidenreich, P. A. (2016). Cost-effectiveness of sacubitril–valsartan in patients with heart failure with reduced ejection fraction. *Ann. Intern. Med.* 165, 681–689. doi:10.7326/M16-0057

Si, L., Winzenberg, T. M., Jiang, Q., and Palmer, A. J. (2015). Screening for and treatment of osteoporosis: Construction and validation of a state-transition microsimulation cost-effectiveness model. *Osteoporos. Int.* 26, 1477–1489. doi:10.1007/s00198-014-2999-4

Solomon, S. D., De Boer, R. A., Demets, D., Hernandez, A. F., Inzucchi, S. E., Kosiborod, M. N., et al. (2021). Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: Rationale and design of the DELIVER trial. *Eur. J. Heart Fail.* 23, 1217–1225. doi:10.1002/ejhf.2249

Thomas, R., and Chalkidou, K. (2016). "Cost-effectiveness analysis," in *Health system efficiency: How to make measurement matter for policy and management*. Editors J. Cylus, I. Papanicolas, and P. C. Smith. (*Copenhagen (Denmark): European observatory on health systems and Policies © world health organization 2016 (acting as the host organization for, and secretariat of, the European observatory on health systems and Policies)*).

Tilyou, S. (2021). Novel agent for HF shows mixed results in large trial [online]. New York: Pharmacy Practice News. [Accessed 11 Feburary 2022].

Tromp, J., Ouwerkerk, W., Veldhuisen, D. J. V., Hillege, H. L., Richards, A. M., Meer, P. V. D., et al. (2022). A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. *JACC. Heart Fail.* 10, 73–84. doi:10.1016/j.jchf.2021.09.004

Tsampasian, V., Baral, R., Chattopadhyay, R., Debski, M., Joshi, S. S., Reinhold, J., et al. (2021). The role of SGLT2 inhibitors in heart failure: A systematic review and meta-analysis. *Cardiol. Res. Pract.* 2021, 9927533. doi:10.1155/2021/9927533

Van Der Pol, S., Degener, F., Postma, M. J., and Vemer, P. (2017). An economic evaluation of sacubitril/valsartan for heart failure patients in The Netherlands. *Value Health* 20, 388–396. doi:10.1016/j.jval.2016.10.015

Weinstein, M. C., and Stason, W. B. (1977). Foundations of cost-effectiveness analysis for health and medical practices. *N. Engl. J. Med.* 296, 716–721. doi:10.1056/NEJM197703312961304

Woods, B., Revill, P., Sculpher, M., and Claxton, K. (2016). Country-level cost-effectiveness thresholds: Initial estimates and the need for further research. *Value Health* 19, 929–935. doi:10.1016/j.jval.2016.02.017

Wu, Y., Tian, S., Rong, P., Zhang, F., Chen, Y., Guo, X., et al. (2020). Sacubitril-valsartan compared with enalapril for the treatment of heart failure: A decision-analytic Markov model simulation in China. *Front. Pharmacol.* 11, 1101. doi:10.3389/fphar.2020.01101

Yao, Y., Zhang, R., An, T., Zhao, X., and Zhang, J. (2020). Cost-effectiveness of adding dapagliflozin to standard treatment for heart failure with reduced ejection fraction patients in China. *Esc. Heart Fail.* 7, 3582–3592. doi:10.1002/ehf2.12844

Yoo, B.-S. (2014). Clinical significance of B-type natriuretic peptide in heart failure. *J. Lifestyle Med.* 4, 34–38. doi:10.15280/jlm.2014.4.1.34

Zakiyah, N., Sinuraya, R. K., Kusuma, A. S. W., Suwantika, A. A., and Lestari, K. (2021). Cost-effectiveness analysis of sacubitril/valsartan compared to enalapril for heart failure patients in Indonesia. *Clin. Outcomes Res.* 13, 863–872. doi:10.2147/CEOR.S322740

Zannad, F., Ferreira, J. P., Pocock, S. J., Anker, S. D., Butler, J., Filippatos, G., et al. (2020). SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: A meta-analysis of the EMPEROR-reduced and DAPA-HF trials. *Lancet* 396, 819–829. doi:10.1016/S0140-6736(20)31824-9

Zueger, P. M., Kumar, V. M., Harrington, R. L., Rigoni, G. C., Atwood, A., Didomenico, R. J., et al. (2018). Cost-effectiveness analysis of sacubitril/valsartan for the treatment of heart failure with reduced ejection fraction in the United States. *Pharmacotherapy* 38, 520–530. doi:10.1002/phar.2108

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 14 October 2022
DOI 10.3389/fphar.2022.1016669

OPEN ACCESS

EDITED BY
Eva Brandl,
Charité Universitätsmedizin Berlin, Germany

REVIEWED BY
Alessio Squassina,
University of Cagliari, Italy
Francisco Abad-Santos,
Universidad Autónoma de Madrid, Spain

*CORRESPONDENCE
Takeo Saito,
saitou@fujita-hu.ac.jp

SPECIALTY SECTION
This article was submitted to Pharmacogenetics and Pharmacogenomics, a section of the journal Frontiers in Pharmacology

RECEIVED 12 August 2022
ACCEPTED 28 September 2022
PUBLISHED 14 October 2022

CITATION
Ninomiya K, Saito T, Ikeda M, Iwata N and Girardin FR (2022), Pharmacogenomic-guided clozapine administration based on HLA-DQB1, HLA-B and SLCO1B3-SLCO1B7 variants: an effectiveness and cost-effectiveness analysis.
Front. Pharmacol. 13:1016669.
doi: 10.3389/fphar.2022.1016669

Pharmacogenomic-guided clozapine administration based on HLA-DQB1, HLA-B and SLCO1B3-SLCO1B7 variants: an effectiveness and cost-effectiveness analysis

Kohei Ninomiya[1], Takeo Saito[1]*, Masashi Ikeda[1], Nakao Iwata[1] and François R. Girardin[2]

[1]Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Aichi, Japan, [2]Division of Clinical Pharmacology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital, Faculty of Medicine, University of Lausanne, Lausanne, Switzerland

The identification of pharmacogenetic factors that increase the susceptibility to clozapine-induced agranulocytosis or granulocytopenia (CIAG) has received increasing interest. The SLCO1B3-SCLO1B7 variant (rs149104283) and single amino acid changes in human leukocyte antigen (HLA) HLA-DQB1 (126Q) and HLA-B (158T) were associated with an increased risk of CIAG. In this study, we evaluated the effectiveness and cost-effectiveness of adding the SLCO1B3-SCLO1B7 to HLA variants as a new pharmacogenomic (PGx) approach and explored the evolution of a cohort of schizophrenic patients taking long-term clozapine as a third-line antipsychotic medication. The decision model included probabilistic and deterministic sensitivity analyses to assess the expected costs and quality-adjusted life-years (QALYs). The current monitoring scheme was compared with the PGx-guided strategy, where all patients underwent pre-emptively a genetic test before taking clozapine, over 10 years. By adding the SLCO1B3-SCLO1B7 variant into HLA variants, CIAG sensitivity increased from 36.0% to 43.0%, the specificity decreased from 89.0% to 86.9%, and the probability of cost-effectiveness improved from 74.1% to 87.8%. The incremental cost-effectiveness ratio was £16,215 per QALY and remained below the conventional decision threshold (£30,000 or US$50,000 per QALY). Therefore, the SLCO1B3-SCLO1B7 variant, as an additional risk allele to HLA variants, increases preemptive test sensitivity and improves the effectiveness and cost-effectiveness of PGx-guided clozapine administration.

KEYWORDS

clozapine, agranulocytosis, granulocytopenia, genotype testing, pharmaco-genomics (PGx), pharmaco-economics, human leukocyte antigen (HLA), schizophrenia

1 Introduction

In most Western and Asian countries, approximately 1%–3% of patients taking clozapine (CLZ) experience severe neutropenia that occurs within several weeks of treatment (J M Alvir et al., 1993). However, drug-induced granulocytopenia and agranulocytosis are distinct phenotypes with different etiologies, risk factors, evolution dynamics, and distinct outcomes. CLZ-induced neutropenia usually occurs after 1–2 weeks of exposure and is more frequent in Africans with low baseline leukocyte count, and the degree of neutropenia depends on the dose and duration. CLZ-induced agranulocytosis (CIA) typically becomes obvious 2–8 weeks after the initiation of therapy, has large idiosyncratic and genetic components, and is more frequent in Asians, females, and the elderly (Flanagan and Dunk, 2008); a low baseline leukocyte count was not associated with CIA.

A genome-wide association study detected that the human leukocyte antigen (HLA) region (single amino acid changes in HLA-DQB1 (126Q) and HLA-B (158T)) (Goldstein et al., 2014) and SLCO1B3-SCLO1B7 (rs149104283) (Legge et al., 2017) were associated with genetic susceptibility to CIA in European ancestry. The association of HLA and *SLCO* alleles with an increased risk of agranulocytosis suggests an immune-mediated mechanism combined with an altered function of drug influx transporter that could affect myeloid precursors translating into CIAG (CIA + CLZ-induced granulocytopenia (CIG)). Influx transporter polymorphisms with altered activity have also been implicated in further adverse reactions of simvastatin-induced myopathy (E. Link et al., 2008) and docetaxel-induced neutropenia (Chew et al., 2012). The SLCO1B3-SCLO1B7 (rs149104283) variant is an intronic single-nucleotide polymorphism to transcripts of the hepatic transporter genes SLCO1B3 and SCLO1B7 (Legge et al., 2017), which could at least partly explain the pharmacokinetic origin of neutropenia.

Pharmacogenomic (PGx) profiles and information could be integrated into clinical settings to reduce CLZ discontinuation for hematological concerns and to improve mental health outcomes. This is particularly topical because current strategies for monitoring leukocyte count in patients taking CLZ remain based on divergent national schemes that are not cost-effective (Girardin et al., 2014). For patients taking CLZ in the US, the UK, Switzerland, and Japan, HLA genotype-guided blood monitoring appeared to be a cost-effective strategy compared with either absolute neutrophil count monitoring or CLZ substitution by other less effective antipsychotics (Ninomiya et al., 2021); (Girardin et al., 2019).

In this study, we investigated whether adding the SLCO1B3-SCLO1B7 variants to the HLA PGx-guided approach is efficient to leverage the performance in predicting CIAG development in patients taking CLZ as a third-line antipsychotic medication.

2 Materials and methods

2.1 Decision analytic model and PGx-guided strategy

We evaluated the effectiveness and cost-effectiveness of adding the SLCO1B3-SCLO1B7 variant (rs149104283) to HLA variants as a new PGx approach in patients taking long-term CLZ (Figure 1).

To compare the results with the current absolute neutrophil count monitoring schemes conducted in the UK as base-case, we used a decision model to explore the evolution of a cohort of adult men and women who received CLZ as a third-line antipsychotic medication.

To assess the model and parameter uncertainty and to test the robustness of findings based on increased PGx test sensitivity (after incorporating the SLCO1B3-SCLO1B7 variant), the Markov model included deterministic and probabilistic sensitivity analyses to calculate the expected costs and quality-adjusted life-years (QALYs) over 10 years. We compared current monitoring schemes with a "PGx-guided strategy," where all patients underwent pre-emptively a genetic test before taking CLZ.

Derived from previous analyses, the decision model was based on two mutually exclusive strategies, namely, the "PGx schedule" and the "common schedule without genetic testing as a standard-of-care" (Ninomiya et al., 2021).

PGx-guided treatment schedule: In this scenario, all patients underwent genetic testing and were divided into two groups based on the presence of risk alleles. The risk of developing CIAG was higher in patients with risk alleles than in those without risk alleles. However, due to the low positive predictive value of this genetic testing (approximately 10%), not all patients with risk alleles developed CIAG. Furthermore, antipsychotic substitution was less efficient in achieving quality of life than clozapine treatment. Thus, having risk alleles does not indicate discontinuation of the CLZ treatment in clinical setting. Therefore, we set up a scenario analysis from the base-case where patients with risk alleles receive clozapine, and it is expected that *a priori* information of the specific patients with genetic risk would alert the psychiatrists' attitude. The overall CIAG onset rate should be reduced with the psychiatrists' awareness of the potential risk and sensitivity to CIAG in these patients. Genetic variants (rs149104283 and HLA-DQB1 (126Q) and HLA-B (158T)) will be considered as additional risk alleles, and prescribers should apply stringent blood monitoring or early "temporary cessation" of CLZ treatment to avoid the "complete discontinuation" of CLZ treatment, which are expected to reduce the overall CIAG onset rate. The CIAG prevention rate was set at 30%, based on previous findings (Ninomiya et al., 2021). Blood monitoring was conducted weekly in the first 18 weeks of CLZ treatment and then every 2 weeks, in accordance with the Clozaril Patient Monitoring Service (CPMS) protocol. If CIAG occurred, CLZ treatment was discontinued and switched to substitute antipsychotic treatment.

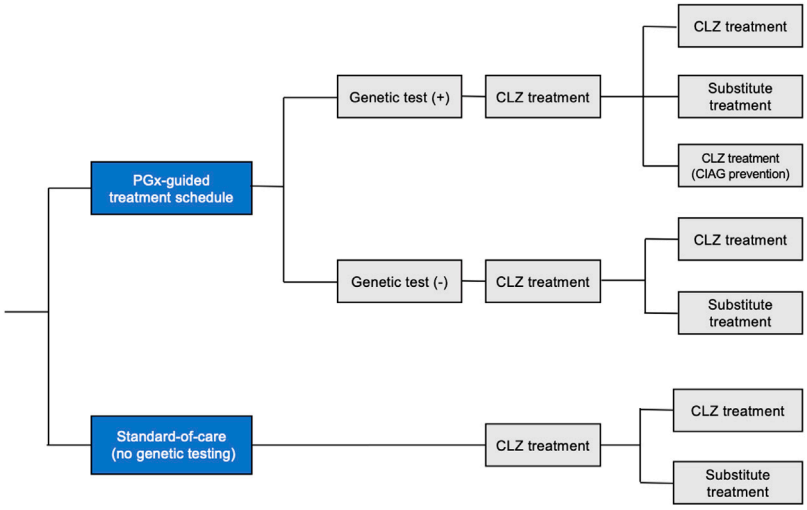

FIGURE 1
Decision tree schematic. The "Standard-of-care (no genetic testing)" compared with the "PGx-guided treatment schedule." CIAG, clozapine-induced agranulocytosis/granulocytopenia.

In the vast majority of cases, patients did not harbor risk alleles and follow the "Standard-of-care (no genetic testing)" (see below).

Standard-of-care (no genetic testing): This corresponds to the current monitoring schedule used in Japan and most Western countries.

In brief, during 18 weeks of CLZ treatment, weekly blood monitoring is performed, and after that, blood monitoring occurs every 2 weeks. However, if the white blood cell count (WBC) or absolute neutrophil count (ANC) decreases to <3,000/mm^3 or 1,500/mm^3, CLZ treatment should be discontinued (rechallenging for patients with CIAG is also prohibited unless the CPMS committee gives permission based on the clinical course) at that moment. The relaxation of the criteria for the entry to the UK CLZ central non-rechallenge database has been modeled recently (Oloyede et al., 2022).

In these models, the possibility of CLZ discontinuation due to WBC cutoff (<3,000/mm^3) was not considered because the definition of "WBC count" does not usually indicate CLZ discontinuation (in such cases, the ANC usually decreased to 1,500/mm^3) (Myles et al., 2018).

All patients received CLZ treatment and if CIAG occurred, CLZ treatment was discontinued and switched to substitutional treatment.

2.2 Population, model structure, and parameters

The target population was identical to that reported previously (Girardin et al., 2019): adult men and women from the UK with treatment resistance schizophrenia who are eligible for CLZ treatment. We used a Markov model for assessing the transition probability (cycle length: 1 month). The model incorporated the health status of the patients to reflect that they received either CLZ or substitute antipsychotic treatments.

Key driving parameters were previously identified: 1) CIAG prevalence (3.43%) (Freeman et al., 2016); 2) cost of treatment for CIAG (£469.48) (Jin et al., 2019); 3) cost of CLZ/day (£1.23) (National Health Service in the UK, 2019)· (Heeg et al., 2008); 4) cost of substitute/day (£5.11), which was calculated by weighting the cost × the percentage of the first-line drugs used in the UK (risperidone: 21.5%, aripiprazole: 10.8%, olanzapine: 19.7%, quetiapine: 42.8%, and amisulpride: 5.2%), because one type of second-generation antipsychotic is commonly prescribed for schizophrenia in the UK (National Health Service in the UK, 2019)· (Patel et al., 2014); 5) cost of genetic tests (£110: we assumed £100 for HLA typing and £10 for rs149104283 genotyping); 6) cost of regular blood test/month (£10.6); 7) utility for patients undergoing CLZ treatment (0.693), which was estimated from the report on the basis of the EQ-5D index score (Sullivan and Ghushchyan, 2006); 8) utility for patients undergoing substitute treatment (0.560), which was estimated from the report on use of standard gamble, rating scales, and paired comparison questions (Revicki et al., 1996); and 9) the CIAG prevention rate [30% (Ninomiya et al., 2021)] (Table 1). The costs related to medical fees were calculated according to the direct Medical Care Expenditure based on the National Health Service in the UK (April 2019) (National Institute of Public Health, 2019).

Aggregated sensitivity and specificity of allelic variants [rs149104283 (Legge et al., 2017), HLA-DQB1 (126Q), and

TABLE 1 Input parameters.

Parameter	Mean	Probabilistic sensitivity analysis	Type of distribution	Distribution parameter	References
CIAG prevalence	3.43%	NO			Freeman et al. (2016)
Cost of treatment CIAG £	469.48	YES	Gamma	alpha:4 lambda:8.5E-3	Jin et al. (2019)
Cost of CLZ/day £	1.23	YES	Gamma	alpha:37.8 lambda:30.75	National Health Service in the UK (2019), Heeg et al. (2008)
Cost of substitute/day £	5.11	YES	Gamma	alpha:104.4 lambda: 20.44	National Health Service in the UK (2019), Patel et al. (2014)
Cost of genetic test £	110	NO			
Cost of regular blood test/month £	10.6	NO			
Utility for patients undergoing clozapine treatment	0.693	YES	Beta	alpha:575 beta:255	Girardin et al. (2019)
Utility for patients undergoing substitute treatment	0.560	YES	Beta	alpha:86 beta:67	Girardin et al. (2019)
CIAG prevention rate	30%	YES	Beta	alpha:24.9 beta:58.1	Ninomiya et al. (2021)
Sensitivity[a]	43.0%	YES	Beta	alpha:169.13 beta:223.87	Legge et al. (2017), Goldstein et al. (2014)
Specificity[a]	86.9%	YES	Beta	alpha:15531.77 beta: 2342.23	Legge et al. (2017), Goldstein et al. (2014)

[a]Based on the combined risk of HLA-DQB1 (126Q) and HLA-B (158T) and rs149104283.
CIAG, Clozapine-induced agranylocytosis/granulocytopenia. CLZ, clozapine.

HLA-B (158T) (Goldstein et al., 2014)] were calculated as follows:

$$Sensitivity = 1 - (1 - Sensitivity1) \times (1 - Sensitivity2)$$
$$= 1 - (1 - 0.360) \times (1 - 0.109) = 0.430$$

Sensitivity1 = sensitivity of HLA-DQB1 (126Q) and HLA -B (158T) = 0.36

Sensitivity2 = sensitivity of rs149104283 = 0.109

$$Specificity = Specificity1 \times Specificity2 = 0.890 \times 0.976$$
$$= 0.869$$

Specificity1 = specificity of HLA-DQB1 (126Q) and HLA -B (158T) = 0.890

Specificity2 = specificity of rs149104283 = 0.976

The outcomes included the mean cost-per-patient and QALY-per-patient for calculating the incremental cost-effectiveness ratio (ICER) for 10 years.

Probabilistic sensitivity analysis was performed using Monte Carlo simulations by varying input parameters (95% confidence intervals or clinically reasonable ranges). We set the number of simulations to 100,000 based on randomly assigned parameters. We obtained the costs and QALY values for both strategies and calculated the ICER based on the following formula:

$$\frac{Cost\ (\textbf{PGx-guided treatment schedule}) - Cost\ (\textbf{Standard-of-care})}{QALY\ (\textbf{PGx-guided treatment schedule}) - QALY\ (\textbf{Standard-of-care})}$$

The discount rate of 3.5% was applied to the costs and QALYs. The cost-per-QALY thresholds were set at £30,000, as recommended in the UK guidelines (National Institute of Public Health, 2019).

The sample size of the combined CLOZUK and CIAG Consortium (CIAC) (229 cases and 13,553 controls) had 80% power to detect a relative risk (RR) > 3 with minor allele frequency (MAF) > 0.10 at $p < 5 \times 10^{-8}$. We defined "undetected risk variants" (RR ≤3; MAF, ≤0.10) that can be a detectable risk by increasing the sample size, with various allele frequencies and relative risks. To estimate the minimum number of cases required, we used the Genetic Association Study Power Calculator (Goncalo, 2017).

The sensitivity and specificity derived from MAF and relative risk for "undetected risk variants" and those from HLA-DQB1 (126Q), HLA-B (158T), and SLCO1B3-SLCO1B7 yielded calibrated sensitivity and specificity estimates. We set the cost for additional genetic tests ranging from £110 to £130 to reflect the probability.

All CEAs followed the Guideline for Preparing Cost-Effectiveness Evaluation to Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline (Husereau et al., 2013).

TreeAgePro® (2019 version, TreeAge Software Inc. MA, United States) was used for the decision model, sensitivity analyses, and simulations.

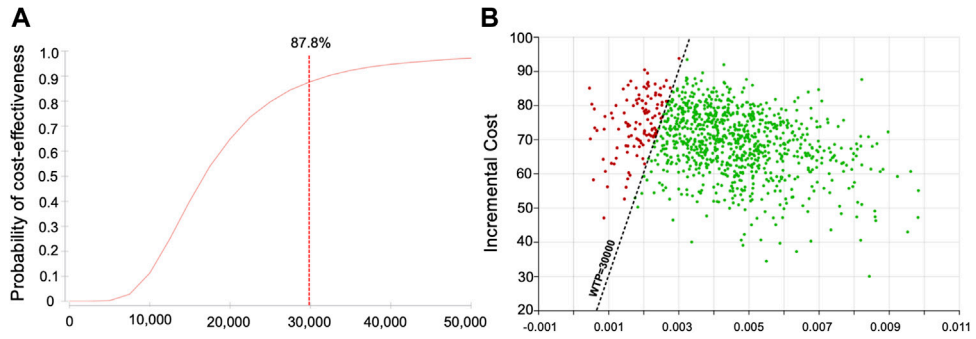

FIGURE 2
Results of probability sensitivity analysis [HLA-DQB1 (126Q), HLA-B (158T) and rs149104283] **(A)** Cost-effectiveness acceptability curve **(B)** Scatter plot for incremental cost and effectiveness: green dots indicate ICERs within willing to pay (WTP) threshold and red dots indicate out of the threshold.

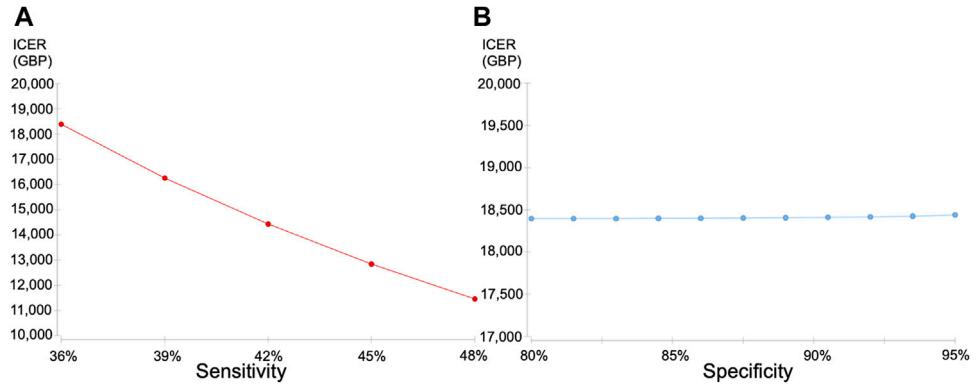

FIGURE 3
Results of one-way sensitivity analysis **(A)** Sensitivity analysis: varying "sensitivities" **(B)** Sensitivity analysis: varying "specificities", ICER incremental cost-effectiveness ratio.

3 Results

Our findings indicated that if the SLCO1B3-SCLO1B7 variant was added to HLA variants, CIAG sensitivity increased from 36.0% to 43.0%, and the specificity decreased from 89.0% to 86.9%. Based on the CIAG incidence of 3.43% and test sensitivity of 0.43, the number of patients needed for genotyping was estimated as follows: (100/(3.43 × 0.43). Overall, 68 screened patients were needed to prevent one case of CIAG and 232 patients were needed to prevent one case of severe CIA (<500/mm^3). These estimates approximate previous estimations with agranulocytosis prevalence but with lower single HLA genotyping sensitivity (Girardin et al., 2019).

From a pharmaco-economic perspective, the probability of cost-effectiveness improved from 74.1% to 87.8%, and the ICER was £16,215 per QALY, indicating that it remained well below the conventional decision threshold (£30,000 or US$50,000 per QALY).

Hence, the PGx-guided schedule appeared as an acceptable alternative to the current blood monitoring schedule (standard-of-care) (Figure 2). To comprehend the effects of specificity reduction, we conducted one-way sensitivity analysis for sensitivity and specificity, respectively (Figure 3). Better ICERs were obtained when we increased the sensitivity; however, the ICERs did not change when various specificities were examined.

We considered a further scenario where the "undetected risk variants" have a relative risk of three and an allele frequency of 5%: we found increased CIAG sensitivity from 43.0% to 56.8% and the specificity decreased from 86.9% to 78.9% by adding the "undetected risk variants" into the HLA and SLCO1B3-SCLO1B7 (rs149104283) variants. Under these hypothetical conditions, the probabilistic estimate of the total cost was

TABLE 2 The number of cases to obtain 80% power under various relative risk and allele frequency of SNPs, and ICER for each model.

Relative risk	Allele frequency	10%	7.5%	5%	2.5%	1%
3.0	Case	230	270	360	640	1,510
	ICER (£/QALY)	8657.73	9959.48	11759.02	14300.20	16539.54
2.5	Case	330	390	530	950	2290
	ICER (£/QALY)	9368.75	10665.39	12391.99	14831.65	16829.12
2.0	Case	570	690	940	1740	4470
	ICER (£/QALY)	10246.28	11518.55	13155.14	15413.00	17142.65

ICER, incremental cost-effectiveness ratio.

£4,278 and that for QALYs was 5.83134 for the PGx-guided strategy. The expected ICER was calculated at £11,819, and the probability of cost-effectiveness was 94.8%, indicating that even under the assumption of further undetected risk alleles, the PGx-guided strategy remained within the acceptable range of cost-effectiveness (Supplementary Figure S1).

Further results and findings associated with an increased relative risk and MAF scenario are provided in Table 2. The number of required cases will be increased obviously if the relative risk and allele frequency decrease. However, it is of note that the ICERs for any relative risk will be smaller than the ICER for the base-case (HLA + SLCO1B3-SLCO1B7 variants), if the MAF is greater than 2.5%.

4 Discussion

To the best of our knowledge, this study is the first comparative cost-effectiveness analysis using two alternative strategies based on pharmacogenomic testing of the SLCO1B3-SCLO1B7 variant in addition to single HLA alleles. Furthermore, as future scenario analysis, if more risk variants will be detected and integrated into this model, even lower ICERs can be obtained as a collateral effect of incorporating additional PGx results.

CIAG or CIA alone impacted the number needed to genotype because the prevalence rates were significantly different (1% vs 3.43%). The pharmacoeconomic findings indicated that the extended PGx approach yielded an ICER of £16,215 per QALY, which remained well below the willing to pay threshold for one additional QALY (i.e., <£30,000/QALY or < US$50,000 per QALY). Furthermore, we used a probabilistic framework to explore joint parameter uncertainty and whether parameter variability is translated into outcome variability to capture the costs and consequences, as shown on the cost-effectiveness acceptability curve (Figure 2): incorporating the SLCO1B3-SCLO1B7 variant to HLA variants improved the probability of cost-effectiveness from 74.1% to 87.8%.

In this model, the genetic test sensitivity, which improved from 36.0% to 43.0%, largely contributed to cost-effectiveness improvement, even though the test specificity decreased marginally from 89.0% to 86.9%. This is supported by our probabilistic sensitivity analyses.

This result also indicates that increasing the "risk" variants improves PGx test sensitivity and cost-effectiveness. As mentioned in Table 2, even small risks have a significant impact on ICER. However, sensitivity limits exist, which largely depend on the novel PGx evidence.

Psychiatrists' prior information for identifying the risk of CIAG could facilitate the use of CLZ, which has economic and clinical benefits for managing patients with treatment-resistant psychosis, such as schizophrenia, or neurodegenerative diseases with extrapyramidal syndromes. Even though the translation processes with clinical implementation of PGx, including proof of effectiveness and cost-effectiveness, have been emphasized (Swen et al., 2007), these findings expand the knowledge for optimizing resource allocation and wisely choosing campaigns (Cassel and Guest, 2012). Moreover, intensive blood monitoring requirements associated with CLZ prescription could delay drug initiation and impede patient recovery. Regulatory agencies, including the Food and Drug Administration, revised the requirements for blood monitoring and dispensing of CLZ with updated risk evaluation and mitigation strategies. Revisions include prescribing CLZ for patients with benign neutropenia and using algorithms and artificial intelligence-based tools for patients who benefited from atypical antipsychotic medications but had CIAG. Recently, a modeling study indicated that the CLZ rechallenging success after patients' hematological parameters falls below particular thresholds, namely, the CLZ central non-rechallenge database (CNRD); the success rates were similar between individuals who did not meet the CNRD registration criteria and those who did meet those criteria (Oloyede et al., 2022).

The limitations of the study, considering preemptive implementation of PGx-guided CLZ prescription, are undoubtedly related to assumptions regarding the consequences of limited test sensitivity. As we considered the SLCO1B3-SCLO1B7 variant, genotyping performance remains the driving parameter for generalizable genetic testing. It is hardly advisable to stop blood monitoring without formal pilot studies and transition

periods. The second limitation is the restricted long-term data in registries: this analysis could not extend beyond 10 years of observation without strong assumptions. Eventually, because we used a third-party payer perspective, we could incorporate neither intangible costs, such as productivity loss related to premature death, nor unintended follow-up benefit.

The study strengths are the key parameters derived from a large CIAG consortium. The decision analytical framework was built using various deterministic and probabilistic sensitivity analyses, with conservative estimates and scenarios, to provide robust results. The costs were derived from hospital statistics and diagnosis-related group rates derived from hospital admissions.

We concluded that adding risk alleles to HLA variants would increase test sensitivity and improve the effectiveness and cost-effectiveness of PGx-guided CLZ administration.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

KN, TS, MI, NI, and FG contributed to the conception and study design. KN, TS, MI, NI, and FG provide substantial contributions to analysis and interpretation of clinical data. KN, TS, MI, and FG wrote the first draft of the article. All authors have contributed to and approved the final version of the manuscript.

Funding

This study was supported by the SRPBS from the Japan Agency for Medical Research and Development (AMED) under Grant Numbers JP20dm0107097 (NI, MI, and TS), JP22wm0425008 (NI, MI, and TS), and JP22wm0525024 (MI); GRIFIN of P3GM from AMED under Grant Numbers JP20km0405201 (TS and NI), JP20km0405208 (MI), JP22tm0424220 (MI); JSPS Kakenhi Grant Numbers JP21H02854 (MI), JP18K15497 (TS), and JP21K07490 (TS); and the Private University Research Branding Project from MEXT (NI). The funders played no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

NI received research support or speakers' honoraria from Sumitomo, Eisai, Daiichi Sankyo, Takeda, Meiji, Tanabe-Mitsubishi, Otsuka, Eli Lilly, Janssen and Viatris.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1016669/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Results of probability sensitivity analysis [HLA-DQB1 (126Q), HLA-B (158T), rs149104283 and "undetected risk variants" (relative risk = 3, minor allele frequency = 5%)] **(A)** cost-effectiveness acceptability curve **(B)** Scatter plot for incremental cost and effectiveness: green dots indicate ICERs within willing to pay (WTP) threshold and red dots indicate out of the threshold.

References

Alvir, J. M., Lieberman, J. A., Safferman, A. Z., Schwimmer, J. L., and Schaaf, J. A. (1993). Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. *N. Engl. J. Med.* 329, 162–167. doi:10.1056/NEJM199307153290303

Cassel, C. K., and Guest, J. A. (2012). Choosing wisely: Helping physicians and patients make smart decisions about their care. *JAMA* 307 (17), 1801–1802. doi:10.1001/jama.2012.476

Chew, S. C., Sandanaraj, E., Singh, O., Chen, X., Tan, E. H., Lim, W. T., et al. (2012). Influence of SLCO1B3 haplotype-tag SNPs on docetaxel disposition in Chinese nasopharyngeal cancer patients. *Br. J. Clin. Pharmacol.* 73 (4), 606–618. doi:10.1111/j.1365-2125.2011.04123.x

Flanagan, R. J., and Dunk, L. (2008). Haematological toxicity of drugs used in psychiatry. *Hum. Psychopharmacol.* 23, 27–41. doi:10.1002/hup.917

Freeman, G. M., Jr., Martin, B. A., and Hu, R. J. (2016). G-CSF dosing to prevent recurrent clozapine-induced agranulocytosis. *Am. J. Psychiatry* 173 (6), 643. doi:10.1176/appi.ajp.2016.15101303

Girardin, F. R., Poncet, A., Blondon, M., Rollason, V., Vernaz, N., Chalandon, Y., et al. (2014). Monitoring white blood cell count in adult patients with schizophrenia who are taking clozapine: A cost-effectiveness analysis. *Lancet. Psychiatry* 1 (1), 55–62. doi:10.1016/s2215-0366(14)70245-7

Girardin, F. R., Poncet, A., Perrier, A., Vernaz, N., Pletscher, M., C, F. S., et al. (2019). Cost-effectiveness of HLA-DQB1/HLA-B pharmacogenetic-guided

treatment and blood monitoring in US patients taking clozapine. *Pharmacogenomics J.* 19 (2), 211–218. doi:10.1038/s41397-017-0004-2

Goldstein, J. I., Jarskog, L. F., Hilliard, C., Alfirevic, A., Duncan, L., Fourches, D., et al. (2014). Clozapine-induced agranulocytosis is associated with rare HLA-DQB1 and HLA-B alleles. *Nat. Commun.* 5, 4757. doi:10.1038/ncomms5757

Goncalo, A. (2017). GAS power calculator. Available: https://csg.sph.umich.edu/abecasis/gas_power_calculator/index.html (Accessed july 1, 2022).

Heeg, B., Buskens, E., Botteman, M., Caleo, S., Ingham, M., Damen, J., et al. (2008). The cost-effectiveness of atypicals in the UK. *Value Health* 11 (7), 1007–1021. doi:10.1111/j.1524-4733.2008.00344.x

Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., Greenberg, D., et al. (2013). Consolidated health economic evaluation reporting standards (CHEERS) statement. *Value Health* 16 (2), e1–e5. doi:10.1016/j.jval.2013.02.010

Jin, H., McCrone, P., and MacCabe, J. H. (2019). Stratified medicine in schizophrenia: How accurate would a test of drug response need to be to achieve cost-effective improvements in quality of life? *Eur. J. Health Econ.* 20 (9), 1425–1435. doi:10.1007/s10198-019-01108-4

Legge, S. E., Hamshere, M. L., Ripke, S., Pardinas, A. F., Goldstein, J. I., Rees, E., et al. (2017). Genome-wide common and rare variant analysis provides novel insights into clozapine-associated neutropenia. *Mol. Psychiatry* 22 (10), 1502–1508. doi:10.1038/mp.2016.97

Link, E., Parish, S., Armitage, J., Bowman, L., Heath, S., Matsuda, F., et al. (2008). SLCO1B1 variants and statin-induced myopathy — a genomewide study. *N. Engl. J. Med.* 359, 789–799. doi:10.1056/NEJMoa0801936(

Myles, N., Myles, H., Xia, S., Large, M., Kisely, S., Galletly, C., et al. (2018). Meta-analysis examining the epidemiology of clozapine-associated neutropenia. *Acta Psychiatr. Scand.* 138 (2), 101–109. doi:10.1111/acps.12898

National Health Service in the UK (2019). Prescription cost analysis - england. Available: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018 (Accessed Apr 1, 2020).

National Institute of Public Health (2019). Guideline for preparing cost-effectiveness evaluation to the central social insurance medical council. Available: https://c2h.niph.go.jp/tools/guideline/guideline_en.pdf (Accessed Dec 26, 2019).

Ninomiya, K., Saito, T., Okochi, T., Taniguchi, S., Shimasaki, A., Aoki, R., et al. (2021). Cost effectiveness of pharmacogenetic-guided clozapine administration based on risk of HLA variants in Japan and the UK. *Transl. Psychiatry* 11 (1), 362. doi:10.1038/s41398-021-01487-4

Oloyede, E., Whiskey, E., Casetta, C., Dzahini, O., Dunnett, D., Gandhi, S., et al. (2022). Relaxation of the criteria for entry to the UK clozapine central non-rechallenge database: A modelling study. *Lancet. Psychiatry* 8, 636–644. doi:10.1016/S2215-0366(22)00188-2

Patel, M. X., Bishara, D., Jayakumar, S., Zalewska, K., Shiers, D., Crawford, M. J., et al. (2014). Quality of prescribing for schizophrenia: Evidence from a national audit in england and wales. *Eur. Neuropsychopharmacol.* 24 (4), 499–509. doi:10.1016/j.euroneuro.2014.01.014

Revicki, D. A., Shakespeare, A., and Kind, P. (1996). Preferences for schizophrenia-related health states: A comparison of patients, caregivers and psychiatrists. *Int. Clin. Psychopharmacol.* 11 (2), 101–108. doi:10.1097/00004850-199606000-00004

Sullivan, P. W., and Ghushchyan, V. (2006). Preference-Based EQ-5D index scores for chronic conditions in the United States. *Med. Decis. Mak.* 26 (4), 410–420. doi:10.1177/0272989X06290495

Swen, J. J., Huizinga, T. W., Gelderblom, H., de Vries, E. G., Assendelft, W. J., Kirchheiner, J., et al. (2007). Translating pharmacogenomics: Challenges on the road to the clinic. *PLoS Med.* 4 (8), e209. doi:10.1371/journal.pmed.0040209

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 17 October 2022
DOI 10.3389/fphar.2022.1031992

OPEN ACCESS

EDITED BY
François R. Girardin,
Centre Hospitalier Universitaire Vaudois (CHUV), Switzerland

REVIEWED BY
Maria C. Katapodi,
University of Basel, Switzerland
Siu Fun Wong,
Chapman University, United States

*CORRESPONDENCE
David Cella,
d-cella@northwestern.edu

SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 30 August 2022
ACCEPTED 03 October 2022
PUBLISHED 17 October 2022

CITATION
Cella D, Chen C-I, Quek RGW, Uribarren A, Reaney M, Mastey V, Collyar D and Chassany O (2022), Patient-reported outcomes labeling for oncology drugs: Multidisciplinary perspectives on current status and future directions.
Front. Pharmacol. 13:1031992.
doi: 10.3389/fphar.2022.1031992

Patient-reported outcomes labeling for oncology drugs: Multidisciplinary perspectives on current status and future directions

David Cella[1]*, Chieh-I Chen[2], Ruben G. W. Quek[2], Ainhoa Uribarren[3], Matthew Reaney[3], Vera Mastey[2], Deborah Collyar[4] and Olivier Chassany[5,6]

[1]Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [2]Regeneron Pharmaceuticals Inc., Tarrytown, NY, United States, [3]IQVIA, Reading, United Kingdom, [4]Patient Advocates in Research (PAIR), Danville, CA, United States, [5]Health Economics Clinical Trial Unit (URC-ECO), Hôpital Hotel-Dieu, Paris, France, [6]Patient-Reported Outcomes Unit (PROQOL), Université de Paris, Inserm, Paris, France

Introduction: Regulatory agencies encourage the incorporation of the patient voices throughout clinical drug development. Patient-Reported Outcomes (PROs) offer one way of doing this and their use has markedly increased in many therapeutic areas, particularly oncology, in recent years. However, few oncology drug labels include PRO data and those which do, offer little consistency.

Objective: To provide multidisciplinary perspectives (patient, pharmaceutical industry, PRO researcher, regulatory expert) on PRO data in oncology drug labels.

Methods: PRO data in the labels of drugs approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for oncology indications between 2010 and 2020 were critically reviewed by authors who provided their insights on the advantages and disadvantages/gaps.

Results: Forty-six oncology drugs included PRO data in their labels. Differences were observed between FDA and EMA PRO labeling (e.g., PRO concept, use of tables and graphs to display PROs or reference to clinical meaningfulness). In providing their perspectives on the number and nature of PROs in labels, authors noted limitations including: the low proportion of oncology drugs with PRO labeling, limited PRO information in labels, lack of patient-friendly language, and potential bias towards positive outcomes. Lack of consistency within- and between-agencies was noted.

Conclusion: Despite regulatory agencies' commitment to incorporate patient voices in regulatory decisions, availability of PRO information is limited in oncology drug labels. While several PRO guidance documents are available from regulatory and Health Technology Assessment agencies, harmonization of PRO guidance for labeling inclusion around the world is needed to better

inform prescribers and consequently their patients in the process of shared medical decisions.

KEYWORDS

quality of life, patient reported outcome instruments, patient care, PRO labeling, oncology

1 Introduction

In the last decade, the weight of patient voices and the release of several official guidelines from the US Food and Drug Administration (U.S. Department of Health and Human Services Food and Drug Administration, 2019) (FDA) and European Medicines Agency (EMA Committee for Medicinal Products for Human Use, 2019) (EMA), strongly encourage sponsors to include Patient-Reported Outcomes (PROs) in clinical trials in many therapeutic areas, particularly in oncology. Inclusion of PROs in the clinical development of new drugs (Bottomley et al., 2019) has long been advocated by patients and healthcare providers to provide a patient-centered holistic understanding of the potential benefits and/or concerns associated with new drugs.

Over the past 10–15 years, systematic consideration and formal incorporation of PRO data into regulatory (U.S. Department of Health and Human Services Food and Drug Administration, 2019; EMA Committee for Medicinal Products for Human Use, 2019; U.S. Department, 2009; FDA, 2017; U.S. Department of Health and Human Services. Food and Drug Administration. Oncology Center of Excellence, 2018) and health technology (Ara and Wailoo, 2011; HAS. Transparency Committee doctrine, 2019; Böhme et al., 2021; Scope et al., 2022) agencies considerations and guidance has increased. The FDA (CDER, 2019) and EMA (EMA, 2019) have expressed interest in the patient perspective in regulatory decision-making in oncology. Specifically, FDA's Center for Drug Evaluation and Research Patient-Focused Drug Development task force drafted four guidance documents to provide a framework and enhance the incorporation of patient voices in medical drug development and regulatory decision making (CDER, 2019). EMA has published their future regulatory science strategy (EMA, 2019) which similarly highlights opportunities to incorporate PROs and patient preferences into drug development and risk-benefit assessment (EMA, 2019). Both agencies have also published oncology-specific PRO guidances (U.S. Department of Health and Human Services Food and Drug Administration, 2019; EMA Committee for Medicinal Products for Human Use, 2019). These guidance documents highlight a role for PROs to inform benefit-risk appraisal for new drugs, and describe the potential inclusion of PRO data in drug labeling (i.e., US Prescribing Information and EU summary of product characteristics) where the evidence supports it. However, while multiple PRO guidelines are available from regulatory and Health Technology Assessment agencies, they are not always consistent. With potential differing regulatory approval standards across regions and countries, guidance surrounding PRO may naturally differ. In addition, Health Technology Assessment agencies and regulatory agencies may have different objectives regarding their assessment of PRO evidence. Nevertheless, a more harmonized approach across regions and agencies is desirable to maximize the utility of data and to ensure that drug development companies have an unambiguous direction to follow during protocol development, endpoint positioning, and pre-specified analyses. Some innovative oncology treatments extend life expectancy; PRO data may provide patients and physicians additional information and context about benefit-risk profile in those settings where several treatment options are available offering similar survival benefit.

PROs are also becoming more important in payer decisions to assess the full value and added value of new therapies. Examples include guidance from the European Network for Health Technology Assessment (EUnetHTA. Guideline, 2013), European Society for Medical Oncology (Dafni et al., 2017) and Institute for Clinical and Economic Review (Institute for Clinical and Economic Review, 2020) which highlight the potential role of PROs in determining the full value of therapies. The Institute for Clinical and Economic Review Value Assessment Framework (Institute for Clinical and Economic Review, 2020) specifies that if PROs have not been collected in the manufacturer's clinical development program, the Institute for Clinical and Economic Review conducts a comprehensive literature review to identify observational studies providing this information (Institute for Clinical and Economic Review, 2020).

In addition to other platforms such as social media, medical literature, Project Patient Voice (PPV) or scientific congresses, the drug label is a potential avenue to communicate the patient experience to physicians and patients to inform prescribing decisions, but few oncology drugs have been granted PRO labeling (ERG, 2019; Gnanasakthy et al., 2019). Such patient experience information in the drug label could be leveraged to develop lay summaries published by the EMA; similar initiatives are underway in the US and in Canada (Barnes and Patrick, 2019). Several hurdles preclude PRO inclusion in labeling, including large amounts of missing data, concern about bias introduced by open label or uncontrolled trial designs, lack of sufficient evidence for the validity of the PRO instrument, and failure to include PROs in the endpoint hierarchy for statistical testing (U.S. Department, 2009; Gnanasakthy et al., 2019; Basch et al., 2015). Furthermore, the label is restricted by space, with limited flexibility to allow for full data description (FDA, 2022).

TABLE 1 Overview of EMA and FDA PRO labeling in oncology.

	FDA	EMA
Number of oncology drugs approved in 2010–2020	108	139
Number of drugs with PRO labeling, n (%)	9[a] (8.3)	42[a] (30.2)
Number of indications with PRO labeling	9	53
PRO concept, n (%)	9	53
HRQoL	0 (0.0)	39 (73.6)
Functioning	0 (0.0)	11 (20.7)
Symptoms	6 (66.7.3)	17 (32.1)
Pain	5 (55.6)	12 (22.6)
Fatigue	1 (11.1)	1 (1.9)
Dyspnea[b]	2 (22.2)	4 (7.6)
Cough	1 (11.1)	3 (5.7)
Diarrhea	0 (0.0)	1 (1.8)
Health utility index	0 (0.0)	11 (20.7)
Patient preference	3 (33.3)	0 (0.0)
Patient-reported use of rescue treatment	2 (22.2)	2 (3.8)
Studies providing PRO data in label	9	57
Double blinded[c], n (%)	4 (44.4)	27 (47.4)
Open label[c], n (%)	4 (44.4)	28 (49.1)
Single arm[c], n (%)	0 (0.0)	1 (1.7)
Unclear[c], n (%)	1 (11.1)	1 (1.7)
Endpoints and analyses[c]	18	63
Primary endpoint, n (%)	2 (22.2)	0 (0.0)
Secondary endpoint, n (%)	5 (55.5)	46 (96.8)
Post-hoc analysis[c], n (%)	0 (0.0)	1 (1.9)
Secondary and exploratory endpoint, n (%)	1 (11.1)	1 (1.9)
Exploratory endpoints, n (%)	1 (11.1)	7 (13.2)

[a]Of these, 5 (9.3%) received PRO labeling by both regulatory agencies.
[b]Also referred to as shortness of breath in several labels.
[c]Among all studies; all other percentages are over the total number of drugs with PRO labeling.
[d]The two instruments most commonly cited in EMA labels.
[e]The two type of instruments most commonly cited in FDA labels.
[f]The diaries included the modified Myelofibrosis Symptom Assessment Form v2.0 diary [fedranitib (FDA), ruxolitinib (FDA)], an electronic diary to capture rescue medication, and severity and frequency of diarrhea and flushing symptoms [lanreotide (FDA)], a diary to capture bowel movements [telotristat ethyl (FDA, EMA)].
[g]The labels (pertuzumab, rituximab, trastuzumab) do not provide any details on the preference questionnaire used in the trials. Abbreviations: EORTC QLQ-C30, European organisation for research and treatment of cancer quality of life questionnaire core; EQ-5D, EuroQoL 5 dimension; PRO, patient-reported outcome.

The current study aims to:

1) Review and appraise PRO data in both FDA and EMA labels of oncology drugs approved between 2010 and 2020; and
2) Conduct an assessment of the PRO data in FDA and EMA labels of oncology drugs. Assessment focused on the (in) consistency, relevance and clarity of PRO data across labels, advantages and disadvantages of PRO data being included in drug labeling, and opportunities for improvement. Each author provided an independent assessment, covering patient, PRO researcher, regulatory expert, and pharmaceutical industry perspectives.

2 Materials and methods

2.1 Identification of patient-reported outcomes labeling in oncology

An initial list of oncology drugs with PRO labeling was obtained from PROLABELS™ (Mapi Research Trust), a database containing PRO data from the US and EU labels published by the FDA and EMA, respectively, where at least one PRO domain and/or instrument is mentioned in the efficacy or safety sections of the main documents (Mapi Research Trust, 2022). Drug approvals, revisions and withdrawals are reviewed daily and updated on the PROLABELS™ database within 1 month (Mapi Research Trust, 2022).

The search was conducted in December 2020. Filters included "neoplasms" for therapeutic area and "PRO" for type of outcome assessment. The FDA US Prescribing Information and the EMA EU summary of product characteristics of oncology drugs approved between January 2010 and December 2020 were reviewed to characterize the PRO labeling in terms of PRO concept (health-related quality of life, patient preference, symptom, functioning, health status), instrument used to assess the PRO, and the format (text and/or table or graphic) and text of the PRO labeling. Irrespective of the number of PRO concepts or endpoints included in the label, a single PRO labeling per drug per indication was used in our metrics. Details of the study design, the endpoint hierarchy and the PRO-related analyses were also captured when available. Drugs approved for oncologic diseases that are considered benign (e.g., leiomyoma) were excluded; overall, four FDA and one EMA labels were excluded. In addition, the label of generics used in oncology and approved during this period were also excluded to avoid double counting. The label of drugs taken off the market were also excluded but biosimilars were not.

2.2 Appraisal of patient-reported outcomes labeling

The PRO data in the labels were reviewed by all authors and critically appraised from their perspectives which included that of patients (n = 1; Collyar), PRO researchers (n = 4; Chassany, Cella, Reaney, Uribarren), pharmaceutical industry (n = 3; Chen, Mastey, Quek), and regulatory experts (n = 1; Chassany). Authors were asked to answer six questions from their perspective(s) (Supplementary Table S1); each author could assess the label from more than one stakeholder standpoint based on their backgrounds. The questions were designed by one of the authors and approved by all authors. Authors provided their insights on the advantages and disadvantages/gaps of PRO data being included in drug labeling (question 1); and (in) consistency of PRO data across labels (question 2). They were also asked how informative and clear PRO data in labels are

TABLE 2 Format used to communicate the PRO labeling.

	FDA (%)	EMA (%)
Text	9	53
Descriptive with no estimates or *p*-values, n (%)	2 (22.2)	37 (69.7)
Descriptive with no estimates or *p*-values but with reference to statistical significance, n (%)	0 (0.0)	7[a] (15.1)
Numerical values, n (%)	7 (77.8)	24 (45.3)
p-values, n (%)	4 (44.4)	15 (28.3)
Reference to whether results were statistically significant or not, n (%)	1 (11.1)	13[b] (35.7)
Reference to clinically meaningfulness, n (%)	0 (0.0)	17 (32.1)
Responder definition, n (%)	2 (22.2)	13 (24.5)
Table, n (%)	2 (22.2)	3 (5.4)
Graph, n (%)	2 (22.2)	0 (0.0)
Bar chart, n (%)	2 (100.0)	0 (0.0)
Waterfall, n (%)	2 (100.0)	0 (0.0)

[a]In addition, three claims reported that the findings were significant but did not specific if they were significant from a statistical point of view.
[b]In addition, nine claims reported that the findings were significant but did not specific if they were significant from a statistical point of view.

(question 3), and about the relevance of the PROs in the labels to them and whether PRO data from labels are used differently compared to PRO data from scientific publications (question 4). Finally, they were asked about improvements they would like to see in PRO labeling (question 5) and other avenues that may be appropriate for communication and presentation of PRO data (question 6). Each author answered the questions independently.

3 Results

3.1 Oncology drugs with patient-reported outcomes labeling

Between 2010 and 2020, out of 169 (FDA: $n = 108$; EMA: $n = 139$) drugs approved in one or more oncology indications, 46 drugs included PRO data for at least one oncology indication in the FDA [$n = 9/108$ (8.3%) drugs in nine indications] or EMA [$n = 42/139$ (30.2%) drugs in 53 indications] labels. Five drugs included PRO data in both, FDA and EMA labels (Table 1; Supplementary Table S2). Among the oncology drugs with PRO labeling approved by EMA between 2010 and 2020, 77% ($n = 41/53$) of them were approved from 2015 onwards. All FDA oncology drugs with PRO labeling were approved from 2014 onwards (data not shown).

PRO concepts in the FDA labeling ($n = 9$) included symptoms in 6 [66.7% with three referring to a single symptom (pain: $n = 2$; short of breath: $n = 1$)], and patient preference in 3 (33.3%) labels (Table 1). PRO concepts in EMA labeling ($n = 53$) included health-related quality of life in 39 (73.6%), functioning in 11 (20.7%), symptoms in 17 (32.1%) and health utility in 11 (20.7%) EU labels (Table 1). The focus on symptoms at FDA is in line with their PRO Guidance (U.S. Department, 2009) which emphasizes the intended and direct effect of treatment (sign/symptom improvement), while the focus on health-related quality of life at EMA is in line with their guidance (EMA Committee for Medicinal Products for Human Use, 2019) emphasizing the relevance of "consequences for the daily life and social functioning" of these core signs and symptoms. The most cited PRO instruments differed largely between FDA and EMA labels, i.e., European Organisation For Research And Treatment Of Cancer core Quality of Life Questionnaire (EORTC QLQ-C30) and the EuroQoL-5 dimensions (EQ-5D) for EMA vs. patient preference questionnaires for FDA (Supplementary Table S3). These differences are unlikely due to differences in the data submitted to these agencies but probably to differing evidence-related standards between FDA and EMA. These differences were also observed for those oncology drugs with PROs in both, the FDA and EMA, label (e.g., pain progression in the FDA abiraterone label for chemotherapy-naïve metastatic castration-resistant prostate cancer vs. pain progression and Functional Assessment of Cancer Therapy—Prostate [FACT-P] total score in its EU label).

In terms of study designs leading to the PRO labeling, 4 (44.4% of nine studies) and 28 (49.1% of 57 studies) were open-label for FDA and EMA approvals, respectively and one EMA approval cited a single arm study (Table 1). Whilst this reflects the oncology trial landscape, with oncology trials more likely to be single arm, open label, and nonrandomized compared to non-oncology trials (Hirsch et al., 2013)—primarily for practical reasons—this is inconsistent with the FDA and EMA stated concerns about interpretability of PRO data when studies are not double-blinded (EMA Committee for Medicinal Products for Human Use, 2019; U.S. Department, 2009).

Although guidance from FDA (U.S. Department, 2009; CDER, 2017) and EMA (EMA. Guideline, 2016) suggests that

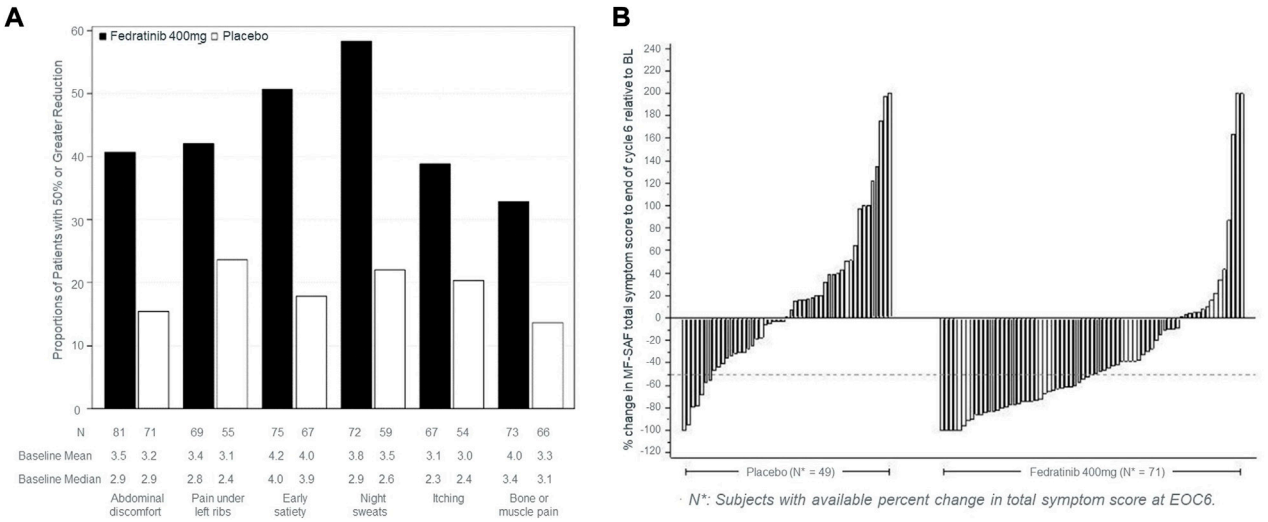

FIGURE 1
Type of graphs used in FDA labels to commnicate PROs. **(A)** Proportion of patients achieving ≥50% reduction in individual symptom scores at the end of cycle six with non-zero baseline scores. **(B)** Percent change from baseline in total symptom score at the end of cycle six for each patient in the phase three study, JAKARTA. The graphs in **(A,B)** were taken from the US product insert of fedranitib (Inrebic®). These two types of graphs are also included in the ruxolitinib (Jakafi®) US product insert.

alpha-controlled endpoints are prioritized for labeling, some labels included text suggesting that the PRO data was derived from exploratory analyses (as a function of being completed *post-hoc* or not being alpha-controlled). It is uncommon for labels to report the endpoint hierarchy or whether the analysis plan was specified with alpha allocation. Based on the label information and further research in the Assessment Reports of EMA approvals, and the clinical and/or Statistical Reviews of FDA approvals, 2 (22.2%) and 8 (15.1%) of the FDA and EMA PRO labelings, respectively, related either exclusively or partly on exploratory endpoint, and 1 (1.9%) of the EMA labelings to *post-hoc* analyses of a secondary endpoint (Table 1). Two of the FDA PRO labelings were based on primary endpoints (patient preference in both cases).

Most FDA (78%) and EMA (94%) PRO labelings were communicated solely as text provided in section 14 ("clinical efficacy") of the FDA label and section 5.1 ("pharmacodynamic properties") of the EMA label. Of the FDA and EMA labels with PRO labeling, only 2 (22.2%) and 3 (5.7%), respectively had a table, and 2 (22.2%) and 0 a graph. The two FDA labels with tables and/or graphs included both (Table 2).

Among FDA labels, tables were used to provide the proportion of patients who improved (fedranitib, ruxolitinib). In EMA labels, tables provided average score at each visit (padeliporfin), change from baseline (mixed model repeated measures for osimertinib), proportion of patients who improved (afatinib) and median time to deterioration (afatinib). Regarding graphs, FDA labels for two drugs (fedranitib; ruxolitinib) each had a bar chart and a waterfall plot (Figure 1).

Among the nine drugs with PRO data in their FDA labels, 2 (22.2%) were descriptive with no numerical data, *p*-value or reference to statistical significance or clinical meaningfulness of the data. *p*-values were reported in four labels (44.4%; Table 2). Two (22.2%) included the threshold used in the responder definition to define within-person meaningful changes and reported the proportion of patients with meaningful changes (all standalone analyses; e.g., "≥50% reduction in Total Symptom Score in 40% in the INREBIC group and 9% in the placebo group" in the fedratinib FDA label).

Among the 53 drugs with PROs in their EU label, PROs were descriptive for 37 (69.8%) of them with no numerical data, or *p*-values, however seven of these EU labels mentioned whether the outcomes were statistically significant or not. Overall, *p*-values were reported for 15 (28.3%) drugs. In addition, 13 (24.5%) reported the threshold used in the responder definition, 2 (3.8%) the proportion of patients with meaningful changes and 17 (32.1%) referred to the clinical meaningfulness of the mean change data [with 10 (e.g., brentuximab and obinutuzumab) of these labels not reporting the threshold; Table 2].

3.2 Multidisciplinary perspectives

3.2.1 Advantages and disadvantages or gaps of patient-reported outcomes data in labeling

Each author, from their collective perspectives, identified between four and nine advantages to having PRO data included in drug labels. The authors generally felt that PRO data inferred meaningfulness to patients (i.e., it was measuring a concept of

TABLE 3 Advantages and gaps of PRO data in drug labeling from different perspectives.

	Patient	Pharmaceutical industry	PRO researcher	Regulatory expert
Advantages of PROs in labeling				
Refer to endpoints that are meaningful to patients (i.e., present patients with data that is relevant to them)	X		X	X
Provide a more holistic perspective of benefit risk drug profile (i.e., incorporate the patient perspective into the appraisal of the drug)		X	X	X
Reflect the humanistic value of drugs to payers (i.e., patient-perceived value on outcomes which are not core to defining safety/efficacy)		X		
Reflect willingness of regulators to capture information deemed important to patients in the label (i.e., patient-focused drug development)			X	
Supplement clinician's assessments with information directly from patients	X			
Informs future use of treatments (i.e., PRO data in the label can be used in treatment decision-making)	X			
Can be used as promotional material (i.e., can be used in direct communication to clinicians and patients)		X	X	
Heterogeneity of PROs in labeling reflects heterogeneity of patient experience within and across diseases (i.e., disease- and treatment-specific strategies encouraged as relevant)	X	X	X	
Gaps of PROS in labeling				
PROs in labeling do not fully capture patients perspective (i.e., often reflect only few of the collected PRO data and thus are insufficiently comprehensive to capture all patient relevant information)[a]	X	X		
Low number of drugs with PRO labeling (i.e., only few drugs with PRO data have these data in the label)	X			
There does not seem to be clear criteria from regulatory bodies for inclusion of PROs in labeling (i.e., apparent inconsistency in labeling decision-making)			X	X
Underrepresentation of certain study designs (e.g., open-label) in PRO claims		X		
Lack of acknowledgement of investment (i.e., cost of developing and/or utilizing PROs does not guarantee use in labeling)			X	
Heterogeneity in labeling across drugs makes it difficult to do meta-comparisons across treatments	X	X	X	
Inconsistencies in core concepts, PROs and/or analyses across studies [i.e., no common data element (CDE) definitions for consistency]	X		X	
Inconsistencies across labels render interpretation of the PRO results difficult for regulators and clinicians				X

The table summarizes the authors responses to question number one of Supplementary Table S1, i.e., "What do you see as the advantages and disadvantages of PRO data being included in drug labeling?" A given author could provide their perspective from different stakeholders.
[a]Because of limited amount of collected PRO data being included in the labeling and because not all PRO tools are appropriate.

interest), providing a more complete perspective of the benefit-risk profile of therapies for patients (see Table 3). Communicating this PRO data through the label reflects a willingness of regulators to reflect the patient perspective in approval documents, encourages consideration by payers, and allows the information to be proactively shared with clinicians and patients; all things perceived as an advantage by the pharmaceutical industry and/or PRO researchers. Having data in label also infers high data quality which can both be used to supplement clinician assessments of treatments and inform use of those treatments in clinical practice—seen as an advantage by the patients (Table 3). The patients, PRO researchers and pharmaceutical industry also discussed the appreciation that different labels reflected different PRO data. While it may be appropriate to consider a core set of outcomes for capturing the patient perspective of oncology medication (U.S. Department of Health and Human Services Food and Drug Administration, 2019), overall PRO strategies must also be considered in light of the specific population, treatment, and study design for a drug development program, with additional non-core outcomes important in certain situations. The wide-ranging PRO label claims (by concept and instrument) was seen as an advantage.

Each author also identified disadvantages or gaps in current PRO labels. These differed across authors. Incomplete PRO data included in labeling may create a false sense of relevance or importance while implying irrelevance for that which is not included, according to patients and the pharmaceutical industry. That is, where multiple PROs were collected to

provide a holistic picture, but where only some of that PRO data is represented in labeling, the overarching impact of treatment on areas important to patients may be missing. While the criteria for defining a PRO measure as "fit for purpose" to support regulatory labeling are well-established (EMA Committee for Medicinal Products for Human Use, 2019), there is a lack of clarity in some cases as to why some PRO label claims have been granted while others have not. This was highlighted from PRO researchers and regulatory expert standpoints.

The lack of consistency in label language was also highlighted and authors were explicitly asked about the impact of this inconsistency across drug labels. Authors acknowledged that different indications, populations and treatment lines may necessitate different approaches to measure outcomes that are important to patients. They also acknowledged the large number of PRO instruments available to oncology researchers. Inclusion of broad concepts in labels was considered as a reflection of the heterogeneity of patient experience within and across diseases, and a sign of regulatory willingness to capture the diversity of relevant patient experiences (Table 3). The authors also acknowledged that different stakeholders have an interest in different concepts. However, this creates difficulties to compare PROs across alternative treatments when conducting (network) meta-analyses; authors highlighted the need to identify core outcome sets or common data elements to assess across studies for PRO instruments (Table 3). Consistency on analytical approaches is also needed. From a regulatory expert perspective, inconsistency limits the possibility to train regulators and clinicians in interpreting PRO results (Table 3). Further, the lack of consistency and valuation of PRO data can create an ill-informed clinical environment, with different information about different concepts being used to make inconsistent decisions and to relay confusing information to patients. It also makes drug development difficult due to lack of clarity and consistency. The pharmaceutical industry may assume a precedent which may be unfounded (e.g., expectations of certain domains or endpoints being better valued by regulatory agencies based on previous PRO labelings); nevertheless, as feasible and as early as possible, pharmaceutical sponsors can and should engage with the FDA review divisions about the acceptability of their PRO endpoints prior to trial initiation. A further gap in PRO labeling from the pharmaceutical perspective is the under-representation of open-label or single-arm study designs.

3.2.2 Clarity of patient-reported outcomes and applicability of patient-reported outcomes in labeling

From the patient and pharmaceutical industry perspectives, PRO data in labeling are not clear, and plain language summaries should be (but rarely are) included to aid interpretation for non-experts (Figure 2A). The lack of clarity means that the data is rarely used in clinical consultations (based on patients' perspective), even though this is one of the goals of the collection of PRO data (Figure 2B). Even for experienced researchers and regulatory experts, it is important to present data in a way that facilitates interpretation of meaningfulness of the PRO findings. Specifically, clinical meaningfulness of the changes observed and the direction of improvement should be better specified in labels and should be consistent with other communications of PRO data, including publications (PRO researchers). More details on the methodology (pharmaceutical industry) and specificity of the data (regulatory expert) are also warranted. In addition, multi-item scales may be more informative than single item scales (PRO researchers) and should be prioritized where clear and easy to interpret (Figure 2A).

Authors considered the applicability of current PRO labeling as limited because they do not capture the full patient experience; only one or few of the concepts assessed in the registrational trials are captured in the label [e.g., labeling restricted to pain using the Brief Pain Inventory for abiraterone in the chemotherapy-naive setting with no reference to any Functional Assessment of Cancer Therapy—Prostate (FACT-P) domains such as prostate cancer symptoms, and impact of prostate cancer on social and family well-being, functional well-being, emotional well-being, physical well-being and quality of life]. All authors considered that when PRO instruments are fit for purpose and data are reliable, the label should include the same PRO endpoints that are communicated in other forums, such as publications (Figure 2B) with appropriate caveats, and that this information should be presented separately from other data to facilitate clarity.

Existing PRO labels are used, in part, to guide pharmaceutical industry and PRO researchers on the PRO strategy development for new drugs; although this information alone is rarely sufficient without understanding and stating the reasons why PROs were or were not included in the label (Figure 2B).

3.2.3 Potential improvements in patient-reported outcomes in labeling

Numerous improvements were proposed by the authors, mainly related to the clarity and consistency of PRO data presentation (see Section 3.2.2), further guidance and transparency in the decision-making process, inclusion of non-traditional PRO data which is important for patient decision-making in clinical practice, and the inclusion of appropriately caveated PRO data from open-label and single arm studies where design constraints are relevant and justifiable (Figure 2C). These study designs are becoming more common in oncology to support accelerated approval (Kanapuru et al., 2017). Additional suggested changes are inclusion of findings that fail to show statistical significance but are clearly explained (opposed to assuming that absence of data indicates a negative finding/lack of data), and language

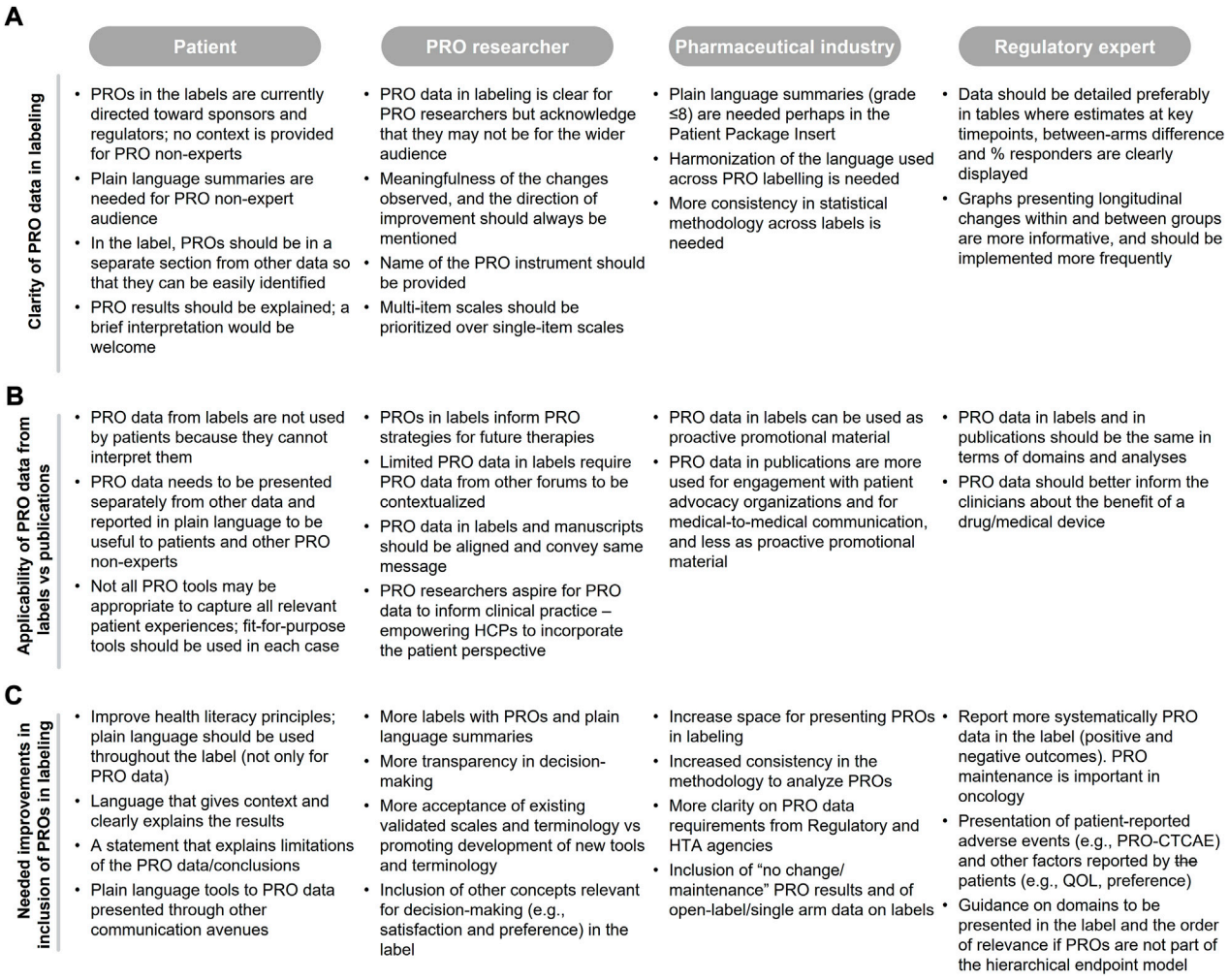

FIGURE 2
Authors feedback on **(A)** clarity of PRO data in labeling, **(B)** applicability of PRO data from labeling PRO data from publications, and **(C)** needed improvements in the context of PRO labeling.

that is more easily interpretable for communication by physicians to patients and caregivers. PROs that may not be eligible for labeling could still be endorsed by regulatory bodies and made available using platforms such as PPV; a pilot online platform launched by FDA in June 2020 to facilitate patients, caregivers and healthcare providers access to patient-reported treatment-related symptom data collected from oncology trials (FDA, 2022). At the time of the review, only one study was included in the PPV website (see Supplementary Material). Effort should also be made to accept and adapt existing validated PRO instruments in the interim rather than solely promoting development of new instruments which often take time for international validation and uptake and may not align with clinical trial schedules (PRO researchers; Figure 2C).

4 Discussion

Our findings suggest that despite the commitments from FDA and EMA to advance patient-focused drug development to capture the patient's voice in clinical research, the role of PROs in regulatory labeling is still suboptimal. Even with the recent increase in the number of drugs with PRO labeling granted by FDA and EMA, the number of drugs with PRO data in the label, and the level of information provided in the label, underrepresents the available PRO evidence for oncology drugs. Unlike clinical endpoints such as overall survival for which all relevant information is generally provided, 22% of FDA and 57% of EMA labels do not provide any numerical estimates or refer to whether the PRO outcomes were statistically and/or clinically meaningful. Difficulty to interpret the PRO data

in the labels has also been reported by others (Gnanasakthy et al., 2022).

Most PRO labeling relate to a single PRO concept, even when the registration trial assessed multiple ones. Inclusion of only selected PRO data may reflect a decision of the drug sponsor to submit partial data only or may result from a regulatory restriction; our analyses are unable to discern between these two possibilities. While it can be argued that not all PRO data may be sufficiently and scientifically robust, relevant, and interpretable to be included in the label, some of these data could also be made available on online platforms such as the FDA's PPV, launched in June 2020 to communicate patient-reported treatment-related symptom data collected from oncology trials that are not included in the FDA label (FDA, 2022). However, since its creation, PPV provides data from only a single trial.

One of the factors that has limited PRO inclusion in labels is the unblinded nature of many oncology studies. Although there is evidence that the potential open-label bias for self-reported outcomes is much smaller than initially considered (Atkinson et al., 2017; Chakravarti et al., 2018; Mouillet et al., 2020; Efficace et al., 2022), and both FDA and EMA have shown willingness to include PRO findings from open-label studies in some oncology and non-oncology labels (Roydhouse et al., 2019), FDA has maintained that patients may provide biased reports of symptoms in trials that are either unblinded, or where study allocation could be revealed by differences in visible side effects between treatment arms (U.S. Department, 2009; Gnanasakthy et al., 2016). EMA is also concerned about potential bias in open label randomized studies but acknowledges that in certain cases the clinical evidence can only be obtained using this study design (EMA Committee for Medicinal Products for Human Use, 2019). Overall, 4 (44%) and 28 (49%) PROs in FDA and EMA labels, respectively, originated from open-label studies.

Another factor precluding inclusion of PRO in labels is failure to include PROs in the analysis hierarchy, often relegating them as exploratory endpoints. However, this does not preclude inclusion of PRO in labels even when the PRO endpoints are not included in the multiplicity hierarchy. PROs in 2 (22%) of the FDA labels were based on either exploratory endpoints or exploratory analyses of secondary endpoints. For EMA approvals, only two labels (sonidegib; vandetanib) specify the exploratory nature of the endpoint, overall the PRO labeling was based on exploratory endpoints only or with secondary endpoints in seven and two cases, respectively. In addition, one PRO labeling (blinatumomab) was based on *post-hoc* analyses of a secondary endpoint. Based on patients feedback, they consider that all endpoints and analyses should be prespecified in the clinical trial protocol. The low number of oncology drugs with PRO data in the label may also be due to the increasing number of oncology trials assessing more than one indication and the challenges to collect PROs in these trials. However, while this may be true in early phase trials, the majority of phase three trials focus on a single indication.

Our appraisal identified several gaps and areas for changes. Lack of plain language in the labeling, difficulty to discern from all other data in the label and use of complex graphs (Brundage et al., 2015), result in an underuse of any label data by clinicians and patients. While the lack of consistency across labels in the reported PRO concepts and analyses reflects the differences in the patient experience across and within oncology diseases, authors highlighted the need to identify core outcome sets and common data elements to be assessed across studies, and to gain agreement on analytical approaches to be taken for consistency. In addition, PROs in labeling often come from blinded comparative studies only and are biased towards positive findings (i.e., improvement). Data from other study types such as open label, single arm or patient preference studies may be informative to patients and healthcare providers, with the right caveats to account for potential biases.

Our study has several limitations. Our findings may not be generalizable to other therapeutic areas or diseases, particularly in those where PROs are often primary endpoints in clinical trials. The recent Eastern Research Group, Inc. review of FDA labels showed that PRO labeling did not exceed 17% of labels in any therapeutic area for new molecule entities approved by FDA between June 2017 and June 2020, and approved by the FDA Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research by 5 February 2021 (ERG, 2019). These percentages are not fully consistent with those reported by Gnanasakthy et al. (2022). The authors observed an important difference in the proportion of new drugs approved by FDA between 2016 and 2020 with PRO labeling across therapeutic areas and in particular between PRO-dependent and PRO-independent therapeutic areas when PRO dependency is defined as diseases that rely on PRO assessments to derive or construct the primary or secondary endpoints for the evaluation of treatment benefit by regulators. The average proportion of labels for PRO-dependent diseases with PRO labeling was 50.0% vs. 9.7% for non-PRO-dependent diseases and 3.2% for oncology labels (Gnanasakthy et al., 2022). The 3.2% is lower than our findings (8.3%) probably because of the exclusion of biosimilars in the Gnanasakthy et al. study. Finally, the number of authors providing perspectives from the different standpoints is not equal across the four stakeholders. While three authors provided their perspectives from a pharmaceutical company and four from a PRO researcher, only one patient gave insights from a patient standpoint and one from a regulatory expert standpoint. The patient and regulator expert's perspectives may not represent the insights of the full patient and regulators communities, respectively.

Our review does not inform on the number of unsuccessful attempts from sponsors in pursuing PRO labeling or reasons for failure. The Eastern Research Group, Inc.'s recent assessment of the use of PROs in FDA labeling shows that only 6% of oncology drugs for which PROs were included in the submission package received PRO labeling (ERG, 2019). This suggests that the low proportion of oncology drugs with PRO data in the label is not

due to PROs being assessed in only few clinical trials. However, future research should investigate the proportion of clinical trials that include PRO collection, the number and variety of instruments included in novel clinical trials, and the proportion of regulatory agencies' reviews that include thoughtful assessment of PROs evidence that may not have led to the incorporation of PRO evidence in drug labels. Our analysis does not provide information on whether PROs were considered in the risk-benefit assessment conducted by FDA or EMA, either. Finally, the current study focused only on PROs; we did not assess the inclusion of other clinical outcome assessments (i.e., clinician-reported, observer-reported or performance outcomes). In our analysis, we also did not identify any oncology drug providing data on caregiver burden despite oncology diseases having a negative impact on caregiver health-related quality of life (Rha et al., 2015).

A strength of this review is that it used a multidisciplinary approach where different stakeholders critically appraised the status quo in PRO labeling. However, future research should also analyze perspectives from treating clinicians and assess if they review and benefit from PRO label data.

The authors acknowledge the great advances incurred in the inclusion of patient voices in regulatory decisions. However, like others (ERG, 2019; Gilead and Regeneron, 2022; Gnanasakthy et al., 2022), we advocate for more inclusion of meaningful patient experience in those decisions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

DaC: Analysis and interpretation of data (equal), drafting and critical review of the manuscript (equal); C-IC: Conceptualization and design (equal), analysis and interpretation of data (equal), drafting and critical review of the manuscript (equal), administrative support (equal); RQ: Conceptualization and design (equal), analysis and interpretation of data (equal), drafting and critical review of the manuscript (equal), administrative support (equal); AU: Acquisition of data (lead), statistical analysis (lead), analysis and interpretation of data (equal), drafting and critical review of the manuscript (equal); MR: Analysis and interpretation of data (equal), drafting and critical review of the manuscript (equal); VM: Conceptualization and design (equal), analysis and interpretation of data (equal), drafting and critical review of the manuscript (equal); DeC: Analysis and interpretation of data (equal), drafting and critical review of the manuscript (equal); OC: Analysis and interpretation of data (equal), drafting and critical review of the manuscript (equal).

Funding

The research was funded by Regeneron Pharmaceuticals, Inc. Authors who are employed by Regeneron also participated in the study design and the analysis and interpretation of findings. The manuscript was written with editorial support from medical writers, funded by the sponsors. All authors were involved at all stages of the manuscript in collaboration with the sponsor company. Medical writing assistance was provided by Montse Casamayor, MD, PhD, and Stephanie Philpott from IQVIA, funded by the study sponsors.

Acknowledgments

The authors wish to thank Dr. Jeff Sloan for his input in the concept of the manuscript.

Conflict of interest

DaC reported being Copyright holder or overseer for FACT/FACIT, PROMIS, and Neuro-QoL. C-IC, RQ, and VM are all employees of Regeneron Pharmaceuticals, Inc. and are shareholders of the company. In addition, RQ owns stocks of Pfizer Inc. and Amgen Inc. AU and MR are employees of IQVIA, which received professional service fees from Regeneron Pharmaceuticals, Inc. for conducting the study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1031992/full#supplementary-material

References

Ara, R., and Wailoo, A. (2011). *NICE decision support unit technical support documents. NICE DSU technical support document 12: The use of health state utility values in decision models*. London: National Institute for Health and Care Excellence. Copyright © 2011.

Atkinson, T. M., Wagner, J. S., and Basch, E. (2017). Trustworthiness of patient-reported outcomes in unblinded cancer clinical trials. *JAMA Oncol.* 3 (6), 738–739. doi:10.1001/jamaoncol.2016.3328

Barnes, A., and Patrick, S. (2019). Lay summaries of clinical study results: An Overview. *Pharm. Med.* 33 (4), 261–268. doi:10.1007/s40290-019-00285-0

Basch, E., Geoghegan, C., Coons, S. J., Gnanasakthy, A., Slagle, A. F., Papadopoulos, E. J., et al. (2015). Patient-reported outcomes in cancer drug development and US regulatory review: Perspectives from industry, the Food and drug administration, and the patient. *JAMA Oncol.* 1 (3), 375–379. doi:10.1001/jamaoncol.2015.0530

Böhme, S., Gerlinger, C., and Huschens, S. (2021). *Patient-reported outcomes in the context of the benefit assessment in Germany*. Available from: https://arxiv.org/ftp/arxiv/papers/2107/2107.03249.pdf.

Bottomley, A., Reijneveld, J. C., Koller, M., Flechtner, H., Tomaszewski, K. A., Greimel, E., et al. (2019). Current state of quality of life and patient-reported outcomes research. *Eur. J. Cancer* 121, 55–63. doi:10.1016/j.ejca.2019.08.016

Brundage, M. D., Smith, K. C., Little, E. A., Bantug, E. T., and Snyder, C. F. (2015). Communicating patient-reported outcome scores using graphic formats: Results from a mixed-methods evaluation. *Qual. Life Res.* 24 (10), 2457–2472. doi:10.1007/s11136-015-0974-y

CDER (2017). *Multiple endpoints in clinical trials guidance for industry. Draft guidance*. Available from: https://www.fda.gov/media/102657/download.

CDER (2019). *Patient-focused drug development*. vailable from: https://www.fda.gov/drugs/development-approval-process-drugs/cder-patient-focused-drug-development.

Chakravarti, P. B., Basch, E. M., Hirshfield, K. M., King-Kallimanis, B., Clark, K. J., Strickland, P. O., et al. (2018). Exploring open-label bias in patient-reported outcome (PRO) emotional domain scores in cancer trials. *J. Clin. Oncol.* 36 (15), e18702–e. doi:10.1200/jco.2018.36.15_suppl.e18702

Dafni, U., Karlis, D., Pedeli, X., Bogaerts, J., Pentheroudakis, G., Tabernero, J., et al. (2017). Detailed statistical assessment of the characteristics of the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) threshold rules. *ESMO Open* 2 (4), e000216. doi:10.1136/esmoopen-2017-000216

Efficace, F., Cella, D., Aaronson, N. K., Calvert, M., Cottone, F., Di Maio, M., et al. (2022). Impact of blinding on patient-reported outcome differences between treatment arms in cancer randomized controlled trials. *J. Natl. Cancer. Inst.* 114 (3), 471–474. doi:10.1093/jnci/djab177

EMA Committee for Medicinal Products for Human Use (2019). *Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man the use of patient-reported outcome (PRO) measures in oncology studies*. EMA/CHMP/292464/2014 2014 [Available from: https://www.ema.europa.eu/en/appendix-2-guideline-evaluation-anticancer-medicinal-products-man-use-patient-reported-outcome-pro.

EMA (2019). *Regulatory science to 2025*. Strategic reflection. EMA/110706/2020.

EMA. Guideline (2016). *On multiplicity issues in clinical trials. Draft*. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-multiplicity-issues-clinical-trials_en.pdf.

ERG (2019). *Assessment of the use of patient experience data in regulatory decision-making*. Final Report 2021 [Available from: https://fda.report/media/150405/Assessment-of-the-Use-of-Patient-Experience-Data-in-Regulatory-Decision-Making.pdf.

EUnetHTA. Guideline (2013). *Endpoints used for relative effectiveness assessment of pharmaceuticals. Health-related quality of life and utility measures*. Final version.

FDA (2017). *Multiple endpoints in clinical trials guidance for industry. Draft guidance*. Available from: https://www.fda.gov/files/drugs/published/Multiple-Endpoints-in-Clinical-Trials-Guidance-for-Industry.pdf.

FDA (2022). *Project patient voice*. Available from: https://www.fda.gov/about-fda/oncology-center-excellence/project-patient-voice.

Gilead, Regeneron (2022). AstraZeneca and more encourage FDA to expand patient reported outcome guidanceAvailable from: https://endpts.com/gilead-regeneron-astrazeneca-and-more-encourage-fda-to-expand-patient-reported-outcome-guidance/.

Gnanasakthy, A., Barrett, A., Evans, E., D'Alessio, D., and Romano, C. D. (2019). A review of patient-reported outcomes labeling for oncology drugs approved by the FDA and the EMA (2012-2016). *Value Health* 22 (2), 203–209. doi:10.1016/j.jval.2018.09.2842

Gnanasakthy, A., DeMuro, C., Clark, M., Haydysch, E., Ma, E., and Bonthapally, V. (2016). Patient-reported outcomes labeling for products approved by the office of hematology and oncology products of the US Food and drug administration (2010-2014). *J. Clin. Oncol.* 34 (16), 1928–1934. doi:10.1200/JCO.2015.63.6480

Gnanasakthy, A., Norcross, L., DeMuro Romano, C., and Carson, R. T. (2022). A review of patient-reported outcome labeling of FDA-approved new drugs (2016-2020): Counts, categories, and comprehensibility. *Value Health.* 25 (4), 647–655. doi:10.1016/j.jval.2021.10.006

HAS. Transparency Committee doctrine (2019). *Principles of medicinal product as-sessments and appraisal for reim-bursement purposes 2020*. [Available from: https://www.has-sante.fr/upload/docs/application/pdf/2019-07/doctrine_de_la_commission_de_la_transparence_-_version_anglaise.pdf.

Hirsch, B. R., Califf, R. M., Cheng, S. K., Tasneem, A., Horton, J., Chiswell, K., et al. (2013). Characteristics of oncology clinical trials: Insights from a systematic analysis of ClinicalTrials.gov. *JAMA Intern. Med.* 173 (11), 972–979. doi:10.1001/jamainternmed.2013.627

Institute for Clinical and Economic Review (2020). *Value assessment framework*. 2020 23 October 2020.

Kanapuru, B., Singh, H., Kim, J., Kluetz, P. G., Food, U. S., and Administration, D. (2017). Patient-reported outcomes (PRO) in cancer trials submitted to the FDA from 2012-2015. *J. Clin. Oncol.* 35 (15), e14024–e. doi:10.1200/jco.2017.35.15_suppl.e14024

Mapi Research Trust (2022). *About PROLABELS*. Available from: https://eprovide.mapi-trust.org/about/about-prolabels.

Mouillet, G., Efficace, F., Thiery-Vuillemin, A., Charton, E., Van Hemelrijck, M., Sparano, F., et al. (2020). Investigating the impact of open label design on patient-reported outcome results in prostate cancer randomized controlled trials. *Cancer Med.* 9 (20), 7363–7374. doi:10.1002/cam4.3335

Rha, S. Y., Park, Y., Song, S. K., Lee, C. E., and Lee, J. (2015). Caregiving burden and the quality of life of family caregivers of cancer patients: The relationship and correlates. *Eur. J. Oncol. Nurs.* 19 (4), 376–382. doi:10.1016/j.ejon.2015.01.004

Roydhouse, J. K., Fiero, M. H., and Kluetz, P. G. (2019). Investigating potential bias in patient-reported outcomes in open-label cancer trials. *JAMA Oncol.* 5 (4), 457–458. doi:10.1001/jamaoncol.2018.6205

Scope, A., Bhadhuri, A., and Pennington, B. (2022). Systematic review of cost-utility analyses that have included carer and family member health-related quality of life. *Value Health.* 25 (22), 164400110–164416533. Online ahead of print. doi:10.1016/j.jval.2022.02.008

U.S. Department (2009). *Of health and human services FDA center for drug evaluation and research*. U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures.

U.S. Department of Health and Human Services Food and Drug Administration (2019). *Core patient-reported outcomes in cancer clinical trials guidance for industry. DRAFT GUIDANCE*. [Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/core-patient-reported-outcomes-cancer-clinical-trials.

U.S. Department of Health and Human Services. Food and Drug Administration. Oncology Center of Excellence (2018). *Center for drug evaluation and research (CDER). Center for Biologics evaluation and research (CBER). Developing and submitting proposed draft guidance relating to patient experience data*. Guidance for Industry and Other Stakeholders. https://www.fda.gov/media/119542/download (Accessed May 10, 2022)

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 26 October 2022
DOI 10.3389/fphar.2022.1019826

OPEN ACCESS

EDITED BY
Matthias Schwenkglenks,
University of Basel, Switzerland

REVIEWED BY
Daniele Mengato,
University Hospital of Padua, Italy
Melania Rivano,
R. Binaghi Hospit, Italy
Xiaohan Hu,
Merck (United States), United States

*CORRESPONDENCE
Ying He,
heying2478@163.com
Yufan Huang,
huangyufan2021@126.com

†These authors have contributed equally to this work

SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 15 August 2022
ACCEPTED 11 October 2022
PUBLISHED 26 October 2022

CITATION
You M, Chen R, Wu Q, Zhu W, He Y and Huang Y (2022), Cost-effectiveness analysis of adebrelimab combined with chemotherapy for extensive-stage small cell lung cancer.
Front. Pharmacol. 13:1019826.
doi: 10.3389/fphar.2022.1019826

Cost-effectiveness analysis of adebrelimab combined with chemotherapy for extensive-stage small cell lung cancer

Maojin You[1†], Ruijia Chen[2†], Qingfeng Wu[1], Wei Zhu[1], Ying He[3*] and Yufan Huang[1*]

[1]Department of Pharmacy, Mindong Hospital Affiliated to Fujian Medical University, Ningde, China, [2]Department of Pharmacy, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, China, [3]Department of Emergency Medicine, Mindong Hospital Affiliated to Fujian Medical University, Ningde, China

Background: The findings of the CAPSTONE-1 trial showed that adebrelimab in combination with chemotherapy (etoposide-carboplatin) (ADCHM) is clinically beneficial as a first-line treatment for patients with extensive-stage small cell lung cancer (ES-SCLC), compared with placebo plus chemotherapy (PLCHM, etoposide-carboplatin). However, owing to the higher cost of adebrelimab, it is unclear whether ADCHM is cost-effective compared with PLCHM. This study aimed to evaluate the cost-effectiveness of ADCHM as a first-line treatment for patients with ES-SCLC from the perspective of the Chinese healthcare system.

Methods: A Markov model with three health states was developed to assess the cost-effectiveness of ADCHM as a first-line treatment option with ES-SCLC. Clinical data were obtained from the CAPSTONE-1 trial. Costs of the drug were calculated at national tender prices, and other costs and utility values were obtained from published literature. The outcomes included life years (LYs), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs). One-way sensitivity analysis and probabilistic sensitivity analysis were used to validate the robustness of the model.

Results: The ADCHM group achieved 1.21 QALYs (2.47 LYs) for $25,312, whereas the PLCHM group achieved 0.81 QALYs (1.59 LYs) for $14,846. The ICER for ADCHM *versus* PLCHM was $25914 per QALY gained. The variables with the greatest impact on the model results were the utility value of progressive disease, the utility value of progression-free survival, and the price of adebrelimab (100 mg). At a willingness-to-pay threshold of $37,653/QALY, ADCHM had an 89.1% probability of being cost-effective compared with PLCHM.

Conclusion: ADCHM may be a cost-effective first-line treatment strategy for ES-SCLC from the perspective of the Chinese healthcare system.

KEYWORDS

cost-effectiveness, adebrelimab plus chemotherapy, extensive-stage small cell lung cancer, first-line treatment, small cell lung cancer

1 Introduction

Worldwide, lung cancer has the second most frequent incidence and is the leading cause of cancer-related mortality, with approximately 1.8 million deaths reported in 2020, i.e., approximately 20% of all cancer deaths (Sung et al., 2021). Small cell lung cancer (SCLC), the most lethal subtype of lung cancer (Oronsky et al., 2017), has a 5-year survival rate of less than 7% (Karachaliou et al., 2016) and accounts for approximately 15% of all lung cancer types (Rudin et al., 2021); nearly two-thirds of SCLC cases progress to the extensive stage at the initial diagnosis (Oronsky et al., 2017). The median overall survival (OS) of patients with untreated extensive-stage SCLC (ES-SCLC) is dismal, at 2–4 months (Liu et al., 2020). Platinum-based drugs combined with etoposide chemotherapy are the standard treatment for ES-SCLC, however, the median OS is merely 9–11 months (Liu et al., 2020). Therefore, developing new treatment regimens for ES-SCLC is an urgent task.

Immune checkpoint inhibitors (ICIs) reduce immunosuppression in the tumor microenvironment and reactivate the anti-tumor function of T cells by inhibiting cytotoxic T lymphocyte-associated protein 4 and programmed cell death-1 pathway/programmed cell death receptor ligand-1 (PD-L1) (Kang et al., 2021). ICIs yield effective results in ES-SCLC treatment (Horn et al., 2018; Paz-Ares et al., 2019; Rudin et al., 2020), bringing new hope for survival among patients with ES-SCLC.

Adebrelimab, an ICI developed in China, is a human anti-PD-L1 monoclonal antibody. Wang et al. (2022) conducted a phase III clinical trial (CAPSTONE-1) in China to estimate the efficacy and safety of adebrelimab combined with chemotherapy (ADCHM) *versus* placebo combined with chemotherapy (PLCHM, carboplatin-etoposide) as the first-line treatment for ES-SCLC. The outcomes showed that as compared to PLCHM, ADCHM significantly improved the OS in previously untreated patients with ES-SCLC.

Although ADCHM offers clinical benefits for patients with ES-SCLC, its high cost limits its widespread use. Therefore, it is essential to evaluate the cost-effectiveness of ADCHM through a pharmacoeconomic approach to estimate the clinical benefits and potential financial consequences of ADCHM for patients with ES-SCLC and determine the rationale for its widespread use in the future. To our knowledge, no economic evaluations of ADCHM treatment for ES-SCLC have been conducted. Our study assessed the cost-effectiveness of ADCHM as a first-line treatment option for ES-SCLC from the perspective of the Chinese healthcare system based on the published results of the CAPSTONE-1 trial (Wang et al., 2022).

2 Materials and methods

2.1 Model construction

The study was designed following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines (Supplementary Table SA) (Husereau et al., 2022). The probabilities of progression-free survival (PFS) and OS were extracted using corresponding Kaplan-Meier survival curves from two treatment groups (ADCHM and PLCHM groups) in the CAPSTONE-1 trial by GetData Graph Digitizer (version 2.26) (Wan et al., 2019; Wang et al., 2022). Statistical analyses were performed using the R software (version 4.2.0) packages, "survival", "survHE", and "survminer." Individual patient data were reconstructed into each Kaplan-Meier curve, and the data were fitted by the survival analysis method described by Hoyle et al. (Hoyle and Henley, 2011). The observation period and subsequent survival functions were obtained by fitting and extrapolating the Kaplan-Meier curves. The distribution functions (including exponential, Weibull, log-normal, and log-logistic) were examined to select the best-fit survival functions using the Akaike information criterion (AIC) and Bayesian information criterion (BIC), i.e., lower AIC and BIC values indicated a better fit (Ishak et al., 2013; Williams et al., 2017), and these values for various survival distribution functions for the PFS and OS curves are shown in Supplementary Table SB. Ultimately, the log-logistic distribution function, $(S(t)= (1+(\lambda t)^{\gamma})^{-1}$; S: survival probability, t: time cycle, λ: scale parameter, and γ: shape parameter), provided the best fit for PFS and OS data and was used to generate corresponding transition probabilities for ADCHM and PLCHM strategies (Table 1).

To simulate the cost and effectiveness of ADCHM as a first-line treatment for ES-SCLC compared with PLCHM, a Markov model was developed using TreeAge Pro 2022 (TreeAge Software, Williams-town, MA, United States). The model included three mutually exclusive health states, namely PFS, progressive disease (PD), and death (Figure 1). The time horizon of the model was 6.9 years (approximately 120 cycles), which was determined by the expected time for 99% of the hypothetical patients modeled to die. The cycle length was 21 days. During each cycle, patients either maintained their assigned health state or progressed to a new health state and were not allowed to return to their previous healthy state. The background mortality in China was not considered in our model, owing to the high lethality of ES-SCLC. According to the method described by Li et al. (2022), the transition probability from the PFS state to the

TABLE 1 The basic parameters of the input model and the range of sensitivity analyses.

Variable	Base value	Range		Distribution	Source
		Min	Max		
Log-logistic survival model of PFS					
ADCHM group					
Scale (λ)	0.1489507	0.119161	0.178741	Log-logistic	Wang et al. (2022)
Shape (γ)	2.070122	1.656098	2.484146	Log-logistic	Wang et al. (2022)
PLCHM group					
Scale (λ)	0.1767604	0.141408	0.212112	Log-logistic	Wang et al. (2022)
Shape (γ)	3.377706	2.702165	4.053247	Log-logistic	Wang et al. (2022)
Log-logistic survival model of OS					
ADCHM group					
Scale (λ)	0.06284631	0.050277	0.075416	Log-logistic	Wang et al. (2022)
Shape (γ)	1.924522	1.539618	2.309426	Log-logistic	Wang et al. (2022)
PLCHM group					
Scale (λ)	0.07650712	0.061206	0.091809	Log-logistic	Wang et al. (2022)
Shape (γ)	2.665497	2.132398	3.198596	Log-logistic	Wang et al. (2022)
ADCHM: Incidence of AEs					
Neutrophil count decreased	0.757	0.606	0.908	Beta	Wang et al. (2022)
White blood cell count decreased	0.461	0.369	0.553	Beta	Wang et al. (2022)
Platelet count decreased	0.383	0.306	0.460	Beta	Wang et al. (2022)
Anemia	0.278	0.222	0.334	Beta	Wang et al. (2022)
PLCHM: Incidence of AEs					
Neutrophil count decreased	0.754	0.603	0.905	Beta	Wang et al. (2022)
White blood cell count decreased	0.379	0.303	0.455	Beta	Wang et al. (2022)
Platelet count decreased	0.336	0.269	0.403	Beta	Wang et al. (2022)
Anemia	0.284	0.227	0.341	Beta	Wang et al. (2022)
Cost ($)					
Neutrophil count decreased	84.21	67.37	101.05	Gamma	Li et al. (2021)
White blood cell count decreased	466.00	372.80	559.20	Gamma	Zhang et al. (2021)
Platelet count decreased	1054.00	843.20	1264.80	Gamma	Peng et al. (2022)
Anemia	508.20	406.56	609.84	Gamma	Zhang et al. (2021)
Carboplatin (100 mg)	4.10	3.28	4.92	Gamma	(Yaozhi Net, 2022)
Etoposide (100 mg)	1.21	0.97	1.45	Gamma	(Yaozhi Net, 2022)
Irinotecan (100 mg)	274.90	219.92	329.88	Gamma	(Yaozhi Net, 2022)
Cisplatin (100 mg)	11.74	9.39	14.09	Gamma	(Yaozhi Net, 2022)
Adebrelimab (100 mg)	25.77	20.62	30.92	Gamma	Yaozhi Net, (2022)
Routine follow-up per cycle	73.86	59.09	88.64	Gamma	Kang et al. (2021)
Tests per cycle	152.09	121.67	182.51	Gamma	Kang et al. (2021)
Best supportive care per cycle	359.00	287.20	430.80	Gamma	Kang et al. (2021)
End-of-life care	2176.00	1740.80	2611.20	Gamma	Kang et al. (2021)
Utility value					
PFS	0.673	0.538	0.808	Beta	Kang et al. (2021)
PD	0.473	0.378	0.568	Beta	Kang et al. (2021)
Disutility due to AEs					
Neutrophil count decreased	0.20	0.16	0.24	Beta	Nafees et al. (2017)
White blood cell count decreased	0.20	0.16	0.24	Beta	Nafees et al. (2017)
Platelet count decreased	0.19	0.15	0.23	Beta	Nafees et al. (2017)
Anemia	0.073	0.058	0.088	Beta	Nafees et al. (2017)

(Continued on following page)

TABLE 1 (*Continued*) The basic parameters of the input model and the range of sensitivity analyses.

Variable	Base value	Range		Distribution	Source
		Min	Max		
Body surface area (m^2)	1.72	1.38	2.06	Normal	Zhang P. F et al. (2020)
Creatinine clearance rate (ml/min)	70	52.5	87.5	Gamma	Liu et al. (2021b)
Discount rate (%)	5	0	8	Fixed	Liu et al. (2011)
Proportion					
Receiving chemotherapy in the ADCHM group	0.40	0.32	0.48	beta	Wang et al. (2022)
Receiving chemotherapy in the PLCHM group	0.52	0.42	0.62	beta	Wang et al. (2022)
Receiving best supportive care in the ADCHM group	0.60	0.48	0.72	beta	Wang et al. (2022)
Receiving best supportive care in the PLCHM group	0.48	0.38	0.58	beta	Wang et al. (2022)

#The price of Adebrelimab is assumed based on the price of sintilimab; ADCHM: adebrelimab in combination with chemotherapy (etoposide-carboplatin); AE, adverse event; PD: progressive disease; PFS: Progression-free survival; PLCHM: placebo plus chemotherapy (etoposide-carboplatin).

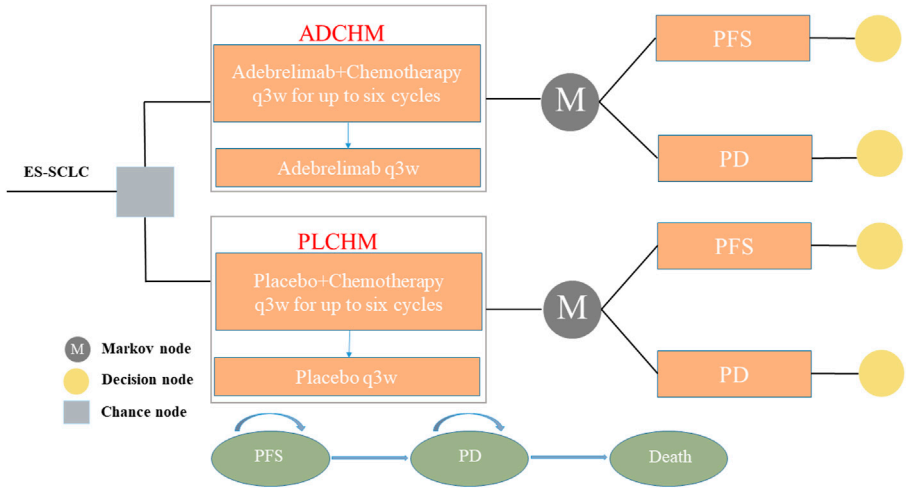

FIGURE 1
The Markov model simulating outcomes for the CAPSTONE-1 trial. All patients with ES-SCLC started with PFS state and received treatment with ADCHM or PLCHM. ADCHM: adebrelimab in combination with chemotherapy (etoposide-carboplatin); ES-SCLC: extensive-stage small-cell lung cancer. PD: progressive disease; PFS: Progression-free survival; PLCHM: placebo plus chemotherapy (etoposide-carboplatin).

death state was assumed as 0 in the Markov model, i.e., there was no direct transition from the PFS state to the death state. Total costs, life years (LYs), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) were the output data obtained from our model. Our cost-effectiveness analysis was conducted from the perspective of the Chinese healthcare system. We set the willingness-to-pay (WTP) threshold at $37,653/QALY (three times the gross domestic product per capita in China in 2021), as recommended by the World Health Organization, and the treatment regimen was considered cost-effective if the ICER was below our predefined WTP threshold.

2.2 Clinical data

Clinical data were extracted from CAPSTONE-1, a phase III randomized controlled clinical trial conducted across 47 tertiary hospitals in China. Patients were enrolled based on the following criteria: 1) 18–75-year-old individuals with histologically or cytologically confirmed ES-SCLC; 2) those who were not treated previously with systemic therapy; 3) Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; 4) Response Evaluation Criteria in Solid Tumors (version 1.1) based inclusion, and at least 3 months of life expectancy (Supplementary Figure SB) (Wang et al., 2022). These patients randomly received ADCHM or PLCHM

regimens. Carboplatin (area under the curve of 5 mg/mL/min) and etoposide (100 mg/m^2 of body surface area) were administered per cycle for up to six cycles. Parallelly, adebrelimab (20 mg/kg) and placebo were administered to patients in the ADCHM group and the PLCHM group, respectively, until disease progression or unacceptable toxicity, for up to 24 months. Treatment with adebrelimab was discontinued in 5.2% of patients in the ADCHM group due to treatment-related adverse events for a median treatment duration of 8 cycles according to the CAPSTONE-1 trial (Wang et al., 2022). Further, to simplify the model, after patients developed disease progression, it was assumed that some patients received second-line chemotherapy (irinotecan + cisplatin), while the remaining received the best supportive care (Table 1). The CAPSTONE-1 trial (Wang et al., 2022) does not report the implementation of second-line chemotherapy, and thus, we utilized the results of Zhao et al. (2019), who conducted a retrospective study for assessing the efficacy of second-line chemotherapy in SCLC patients whereby the first-line standard therapy failed, to estimate the duration of chemotherapy (approximately 3.6 cycles) required for these patients. Each patient received the best supportive care after the failure of second-line therapy. In the CAPSTONE-1 trial, the median age of the patients was 62 years; therefore, we assumed a body surface area of 1.72 m^2 (weight, 65 kg; height, 1.64 m) and a creatinine clearance rate of 70 ml/min to set the administration dose (Goulart and Ramsey, 2011; Zhu et al., 2018; Wang et al., 2022).

2.3 Costs and utilities

We only considered the direct medical costs, including the cost of drugs, tests, follow-up, end-of-life care, and management of adverse reactions of grade 3 or higher with an incidence greater than 5% (Table 1). The cost of drugs was obtained from the national tender prices (Yaozhi Net, 2022). However, adebrelimab is not yet on the market, and thus, we could not obtain its exact price. We estimated the plausible price of adebrelimab in China (converted to the price required per cycle) based on the price of sintilimab (Yaozhi Net, 2022), a drug developed in China ($334.9/200 mg). Other costs were sourced from published literature and adjusted to the prices in 2021 using the China Statistics Bureau Medical Price Index (National Bureau of Statistics, 2021). All costs were converted using the average exchange rate in 2021 and expressed in US dollars ($1 = 6.45 RMB). It should be pointed out that apart from body weight, body surface area, and creatinine clearance, no other parameters can affect the cost of drugs. As the relevant data on the quality of life were not available in the CAPSTONE-1 trial (Wang et al., 2022), the utility of PFS and PD was assessed from published literature in China (Table 1) (Kang et al., 2021). We considered the disutility of adverse reactions of grade 3 or higher with an incidence greater than 5% to reduce the impact of using the same utility values for both treatment groups in the model. Both costs and health utilities were discounted, and the discounted values were set at 5% per year (Table 1) (Liu et al., 2011).

2.4 Sensitivity analysis

To examine the robustness of the model, we conducted sensitivity analyses, including one-way and probabilistic sensitivity analysis (PSA). We performed a one-way sensitivity analysis for each variable to determine the factors that directly affected the ICER and the final results were presented in a tornado diagram. We adjusted the variables within a given range (Table 1). The range of all variables was their 95% CIs derived from the literature or assumed to be ± 20% of the baseline value in cases of lack of data. The lower and upper bounds of the discount rate were set at 0% and 8%, respectively (Liu et al., 2011). In PSA, to verify the effects of the parameters on the uncertainty of the results, 1,000 iterations were performed in the Monte Carlo simulations with all parameters assigned to appropriate distributions in the model. All probability and health utility parameters were assigned the beta distribution. The costs and creatinine clearance rates were assigned the gamma distribution. The body surface area was assigned the normal distribution. The relevant parameters in the distribution of PSA were calculated based on the baseline values and ranges of variation for the parameters (Table 1). Simultaneously, we repeated the calculation of the acceptable probabilities of cost-effectiveness with ADCHM by continuously increasing the price of adebrelimab. When the acceptable probability was less than 50%, at that point ADCEHM was no longer considered cost-effective as the first-line treatment for ES-SCLC as compared to chemotherapy. We used the prices of available imported ICIs, including pembrolizumab ($2777.98/100 mg) and nivolumab ($1434.11/100 mg) (Yaozhi Net, 2022), as the reference for adebrelimab to calculate the acceptable probabilities for ADCHM (converted by the dose required for one cycle). The results of PSA are represented as scatter plots and cost-effectiveness acceptability curves.

2.5 Subgroup analysis

Subgroup analyses were performed to assess the uncertainty in outcomes owing to different patient characteristics, including sex, age, ECOG performance status, smoking history, lactate dehydrogenase concentration at enrolment, liver metastases, brain metastases, disease stage, and PD-L1 tumor proportion score (Table 2). Due to the lack of sufficient survival data for each subgroup, for subgroup survival extrapolation, we assumed that all subgroups in the PLCHM group had the same survival

TABLE 2 Results of subgroup analyses.

Subgroup	PFS HR (95% CI)	OS HR (95% CI)	ICER ($/QALY)	Cost-effectiveness probability (%)
Sex				
Male	0.72 (0.57–0.90)	0.72 (0.57–0.92)	30357	73.7
Female	0.55 (0.33–0.90)	0.62 (0.37–1.05)	24584	87.9
Age				
<65 years	0.70 (0.54–0.91)	0.71 (0.54–0.93)	29505	77.1
≥65 years	0.62 (0.43–0.89)	0.70 (0.48–1.00)	26978	82.1
ECOG performance status				
0	0.62 (0.35–1.10)	0.83 (0.46–1.52)	30188	67.1
1	0.69 (0.56–0.87)	0.69 (0.55–0.87)	28657	78.1
Smoking history				
Current or former smoker	0.76 (0.60–0.96)	0.75 (0.59–0.95)	32887	63.4
Never smoked	0.44 (0.27–0.71)	0.59 (0.37–0.95)	21697	93.7
LDH concentration at enrolment				
≤ULN	0.70 (0.52–0.95)	0.59 (0.42–0.82)	27243	81.8
>ULN	0.64 (0.48–0.85)	0.83 (0.62–1.11)	29593	74.4
Liver metastases				
Yes	0.74 (0·51–1.07)	0.92 (0.65–1.31)	41617	46.3
No	0.64 (0.50–0.83)	0.61 (0.46–0.81)	26167	86.5
Brain metastases				
No	0.65 (0.53–0.81)	0.68 (0.55–0.85)	27283	85.1
Disease stage				
IV	0.68 (0.55–0.83)	0.72 (0.58–0.90)	28909	80.6
PD-L1 tumour proportion score				
<1%	0.68 (0.54–0.85)	0.66 (0.52–0.83)	27822	80.2
≥1%	0.70 (0.34–1.45)	0.72 (0.33–1.59)	33099	63.1

ECOG, eastern cooperative oncology group; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PD-L1, programmed cell death receptor ligand-1; PFS, progression-free survival; QALY, quality-adjusted life years; ULN, upper normal limit.

function (log-logistic survival model) for PFS and OS and estimated the PFS and OS survival function for each subgroup of the ADCHM group based on the subgroup-specific hazard ratios (Table 2) extracted from the results of the CAPSTONE-1 trial (Wang et al., 2022), according to the method described by Hoyle et al. (2010). The ICERs and probabilities of cost-effectiveness acceptability were calculated for each subgroup. In the subgroup analysis, we did not change other parameters except for the subgroup-specific hazard ratios.

3 Results

3.1 Base case analysis

The results of our study are expressed as LYs, QALYs, and ICER. The ADCHM group achieved 2.47 LYs and 1.21 QALYs at $25,312. In the PLCHM group, the effectiveness was 1.59 LYs and 0.81 QALYs at $14,846. The average incremental effectiveness and cost in the ADCHM group were 0.40 QALYs, and $10,466 respectively, relative to those in the PLCHM group. The ICER for ADCHM *versus* PLCHM was $25,914 per QALY gained (Table 3). At the WTP threshold of $37,653/QALY in China, ADCHM emerged as a more cost-effective treatment strategy than PLCHM.

3.2 Sensitivity analysis

3.2.1 One-way sensitivity analysis

The outcomes of the one-way sensitivity analysis based on the model are presented in the tornado diagram (Figure 2), and the most influential variables were the scale parameter value of the PFS state in the PLCHM group, the utility value of PD, and the scale parameter value of the PFS state in the ADCHM group. Despite changing the values of these parameters, the ICER remained consistently below our predetermined WTP threshold. The variables exerting a relatively small impact on

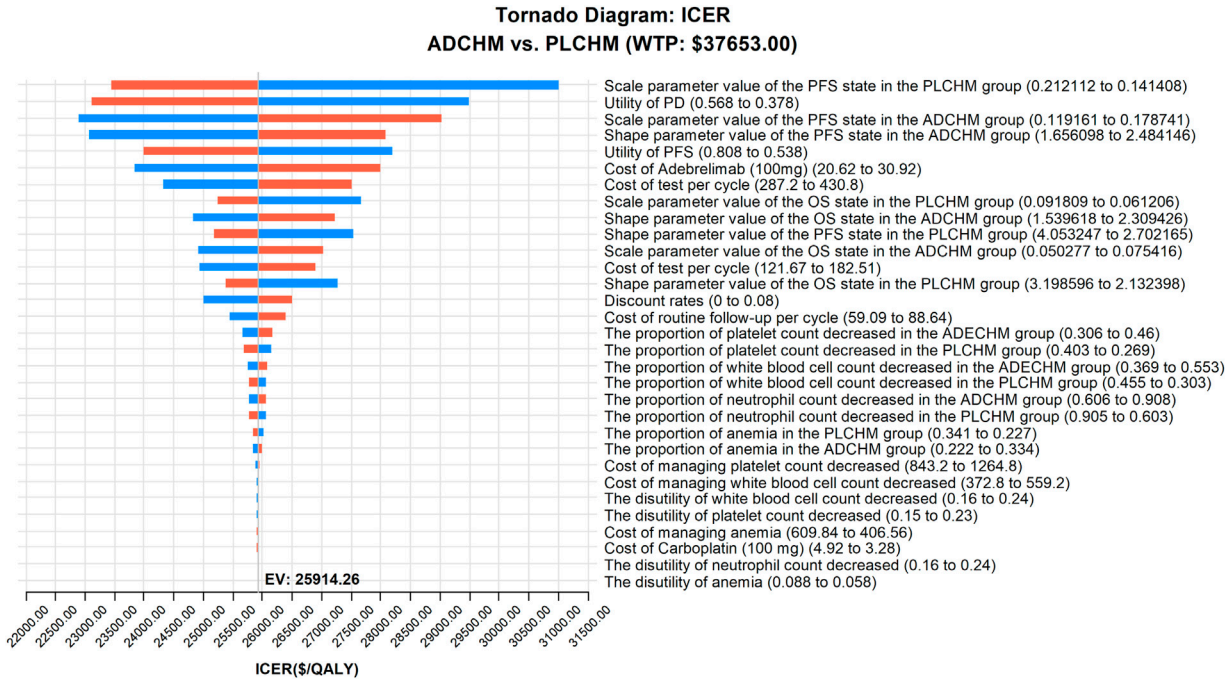

FIGURE 2
One-way sensitivity analyses of ADCHM in comparison with PLCHM. ADCHM: adebrelimab in combination with chemotherapy (etoposide-carboplatin); ES-SCLC: extensive-stage small-cell lung cancer; ICER: incremental cost-effectiveness ratio; PD: progressive disease; PFS: Progression-free survival; PLCHM: placebo plus chemotherapy (etoposide-carboplatin).

the results were the shape parameter value of the PFS state in the ADCHM group, the utility value of PFS, and the price of adebrelimab (100 mg).

3.2.2 PSA

The results of the PSA are presented in the scatter plot (Figure 3) and the cost-effectiveness acceptance curve (Figure 4). The probability that the ADCHM group was cost-effective as compared to the PLCHM group when the WTP threshold was $37,653/QALY was 89.1%. The probability of cost-effectiveness of ADCHM was 74.1% when the cost of adebrelimab (100 mg) was set at 1.5 times its original price. When adebrelimab (100 mg) was priced at $55.40, 2.15 times its original price, the probability that ADCHM treatment for ES-SCLC remained cost-effective as compared to PLCHM was 50%. When the market price of pembrolizumab or nivolumab was used as the reference for adebrelimab, the probability of ADCHM's cost-effectiveness relative to PLCHM was 0.

3.3 Subgroup analyses

For most subgroups, the ICER for the ADCHM group as compared to the PLCHM group was below the WTP threshold of $37,653/QALY, ranging from $21,697/QALY in patients who never smoked (probability of cost-effectiveness, 93.7%) to $33099/QALY for PD-L1 tumor proportion score ≥1% (probability of cost-effectiveness, 63.1%). Only in the subgroup of patients with liver metastases, the ICER of the ADCHM group as compared to that of the PLCHM group was higher than $37,653/QALY, reaching $41,617/QALY (probability of cost-effectiveness, 46.3%) (Table 2).

4 Discussion

According to the guidelines for the management of primary lung cancer (The General Office of the National Health and Health Commission, 2022), chemotherapy (etoposide combined with carboplatin or cisplatin) in combination with a PD-L1 inhibitor is recommended as the first-line treatment for patients with ES-SCLC. To our knowledge, only three studies have evaluated the cost-effectiveness of combination chemotherapy with PD-L1 inhibitors as a first-line regimen for ES-SCLC from the perspective of the Chinese health system (Li et al., 2019; Liu and Kang, 2022; Tong et al., 2022). However, their results suggest that PD-L1 inhibitor combination chemotherapy is

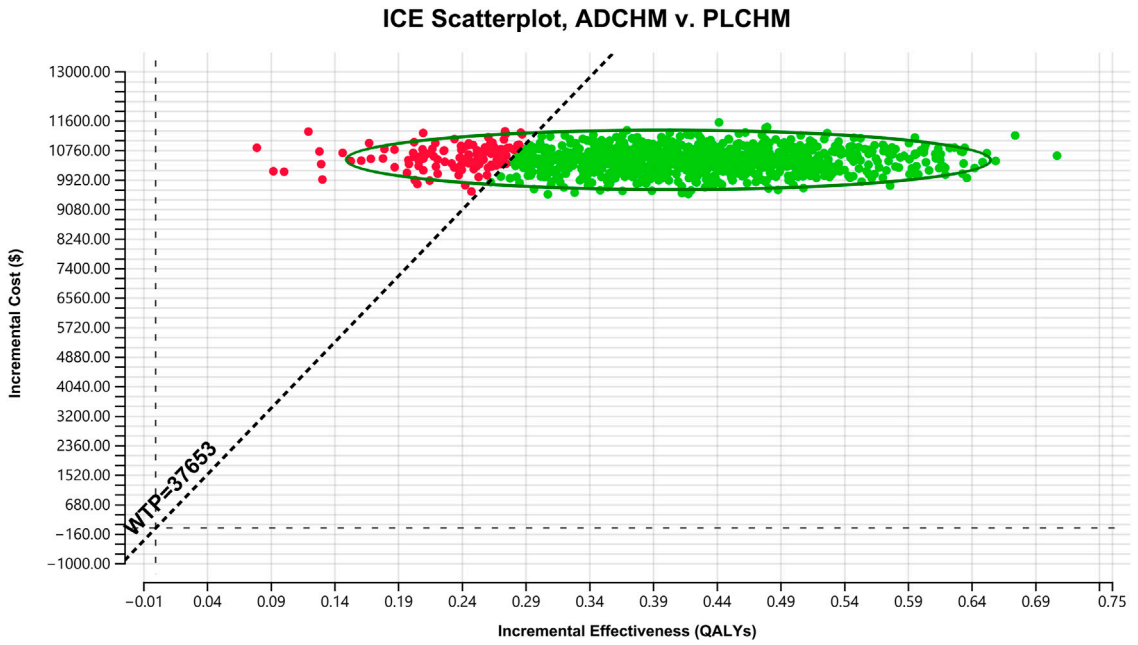

FIGURE 3
A probabilistic scatter plot of the ICER between the ADCHM group and the PLCHM group. Each point means the ICER for 1 simulation. Ellipses are used to indicate 95% confidence intervals. Points that lie below the ICER threshold represent cost-effective simulations. ADCHM: adebrelimab in combination with chemotherapy (etoposide-carboplatin); PLCHM: placebo plus chemotherapy (etoposide-carboplatin); QALYs, quality-adjusted life years; ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay.

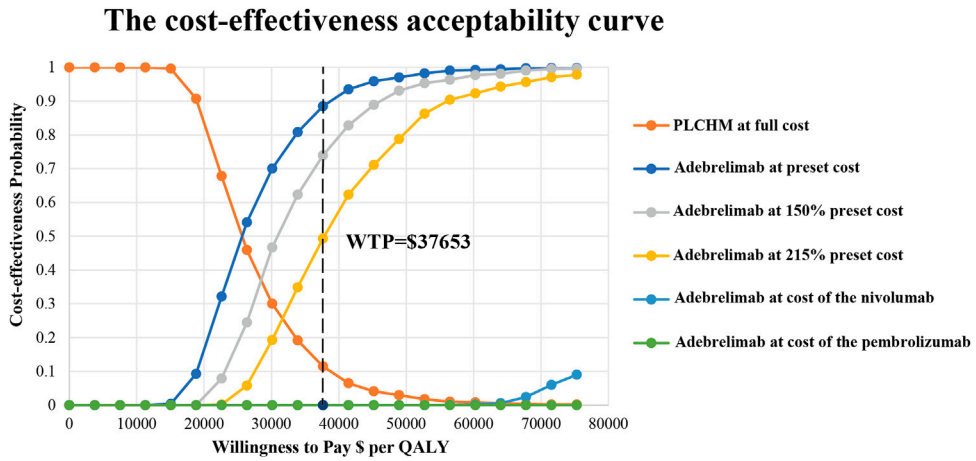

FIGURE 4
The cost-effectiveness acceptability curves for the ADCHM treatment option compared with the PLCHM treatment option. ADCHM: adebrelimab in combination with chemotherapy (etoposide-carboplatin); PLCHM: placebo plus chemotherapy (etoposide-carboplatin); QALY, quality-adjusted life year; WTP: willingness-to-pay.

unlikely to be cost-effective for ES-SCLC. Several studies (Zhou et al., 2019; Zhang L et al., 2020; Liu et al.,2021a; Ding et al., 2021; Lin et al., 2021; Wang et al., 2021; Zhu et al., 2021) evaluated the economics of PD-L1 inhibitor from a perspective outside of China showing that PD-L1 inhibitor combined with chemotherapy as the first-line regimen for ES-SCLC is not cost-effective as compared to chemotherapy, whereby the price of the PD-L1 inhibitor has a significant impact on the outcomes of the model, consistent with the findings in China.

TABLE 3 Effectiveness and costs obtained from the model.

Regimen	PLCHM	ADCHM	Incremental
Total cost, $	14,846	25,312	10,466
Overall LYs	1.59	2.47	0.88
Total QALYs	0.81	1.21	0.40
ICER, $			
Per LY			11,851
Per QALY			25,914

ADCHM: adebrelimab in combination with chemotherapy (etoposide-carboplatin); ICER: incremental cost-effectiveness ratio; LY: life year; PLCHM: placebo plus chemotherapy (etoposide-carboplatin); QALY: quality-adjusted life year.

A key factor that makes PD-L1 inhibitor plus chemotherapy a cost-effective option for treating ES-SCLC as compared to chemotherapy alone is the price of PD-L1 inhibitors in China. We inferred that the price of adebrelimab confers a great advantage over other PD-L1 inhibitors imported from abroad as it is an indigenously-developed PD-L1 inhibitor in China. In the CAPSTONE-1 trial (Wang et al., 2022), Wang et al. used adebrelimab for the first time as a first-line treatment option for patients with ES-SCLC, and their results suggested that ADCHM as compared to PLCHM as a first-line treatment option significantly improved the OS of previously untreated ES-SCLC patients. The median OS was significantly longer in the ADCHM group relative to the PLCHM group (15.3 months vs. 12.8 months, respectively); OS was higher in the ADCHM group than in the PLCHM group at both 12 and 24 months. The ADCHM group showed a reduced risk of progression or death, a higher objective remission rate, and a longer duration of remission. The safety of the combination of adebrelimab and chemotherapy was manageable, with a low incidence of treatment discontinuation due to adverse events. Thus, adebrelimab, a PD-L1 inhibitor, is a potential therapeutic option for ES-SCLC. However, the high prices of PD-L1 inhibitors (including adebrelimab) have significantly increased healthcare costs, thereby making them an uneconomical treatment option, especially in countries with limited healthcare resources, such as China. Therefore, it is essential to evaluate the cost-effectiveness of ADCHM for ES-SCLC. Based on the results of the CAPSTONE-1 trial (Wang et al., 2022), our findings suggested that ADCHM is a cost-effective first-line treatment option for ES-SCLC as compared to PLCHM. The results of the subgroup analysis showed that most subgroups of patients preferred treatment with ADCHM owing to >50% probability of cost-effectiveness as compared to PLCHM, except for subgroups with liver metastases. This is beneficial for patients with ES-SCLC, as it is the first cost-effective treatment option with PD-L1 inhibitors, a major innovative point highlighted in our study.

We were unable to obtain the price of adebrelimab because it is not yet on the market. The price of adebrelimab in our model was assumed based on the price of other indigenously developed PD-L1 inhibitors in China. Therefore, we varied the price of adebrelimab to obtain different results for the cost-effectiveness of ADCHM for treating ES-SCLC. The different cost-effectiveness results obtained from the different price settings for adebrelimab are expected to provide an important reference for the Chinese health insurance authorities when negotiating the price of adebrelimab. The results of the probabilistic sensitivity analysis showed that ADCHM would no longer remain a cost-effective treatment option if the price of adebrelimab (100 mg) goes beyond $54.40.

The selection of comparators in the model is an important issue to consider when performing a cost-effectiveness analysis. The combination of durvalumab or atezolizumab with chemotherapy as a first-line treatment option for ES-SCLC has been approved by the Food and Drug Administration but this was not assessed in our study (Oronsky et al., 2022). From a Chinese perspective analysis, neither treatment option is cost-effective compared to chemotherapy (Li et al., 2019; Liu and Kang, 2022; Tong et al., 2022). Liu et al. (Liu and Kang, 2022) concluded that durvalumab would require a 90% price reduction to remain cost-effective in the presence of the patient assistance program, while a larger price reduction would be required in the absence of the assistance program. Similarly, Li et al. (2019) concluded that atezolizumab would require a price reduction of 80% or more to become cost-effective. They did not consider the important context of the medical insurance reimbursement, which is consistent with our understanding from the Fujian Provincial Medical Insurance Bureau (http://ybj.fujian.gov.cn/) that neither dulvalumab nor atezolizumab is included in the medical insurance reimbursement list. Thus we believe it is reasonable to select chemotherapy as a comparator for the cost-effectiveness analysis of ADCEHM.

Our study has some limitations. First, owing to the lack of long-term survival data, we used a log-logistic survival model to infer survival tails beyond the observed time horizon, which may not accurately reflect real-world settings. Our cost-effectiveness analysis will be updated when long-term survival data are reported. Second, when patients experience disease progression, we placed some of them on second-line chemotherapy and others on best supportive care due to the lack of relevant survival data for the enrolled patients. Additionally, the duration of second-line chemotherapy was based on the findings of Zhao et al. (2019). This may not accurately reflect the current clinical practice conditions. We will analyze this issue further when relevant treatment costs and survival data for patients after progression are available. Third, we only considered adverse reactions of grade 3 or higher with a probability of occurrence greater than 5% in the model. We assumed that low-probability adverse events would not alter our conclusions. Sensitivity analyses also showed that the results of the model were insensitive to the parameters associated with adverse reactions (including incidence, cost of management, and disutility). Fourth, to simplify the model, we assumed a patient weight of 65 kg, a body surface area of 1.72 m^2, and a creatinine clearance rate of 70 ml/min; one-way sensitivity analyses showed that the

model results were insensitive to these parameters. Fifth, patients were allowed to undergo prophylactic cranial irradiation during the maintenance phase of treatment but prophylactic cranial irradiation was not included in this model owing to the small number of patients receiving brain irradiation in the CAPSTONE-1 trial and the lack of relevant treatment data. Sixth and the biggest limitation of the model is the lack of the actual price of adebrelimab since it is not yet available; we shall update our analysis when the price of adebrelimab is available. Seventh, we did not consider the direct transition from the PFS state to the death state in the Markov model, which may have an inevitable effect on the results of our model. Finally, we assumed that the survival function was consistent for all subgroups in the PLCHM group and constructed the survival function for each subgroup in the ADCHM group from subgroup-specific hazard ratios, which differed from the true survival function, owing to the lack of Kaplan-Meier survival curves for all subgroups in the CAPSTONE-1 trial. This subgroup analysis is an exploratory study, and thus, the results should be interpreted with caution. Despite these limitations, our findings provide a valuable reference for Chinese policymakers for formulating first-line treatment for advanced or metastatic ES-SCLC.

5 Conclusion

At present, ADCHM is not recommended as a first-line treatment option in the relevant ES-SCLC guidelines, as it is still under institutional evaluation. However, from the perspective of the Chinese healthcare system, our findings suggest that ADCHM is a cost-effective treatment option as the first-line treatment for ES-SCLC as compared to conventional chemotherapy. Our results provide an important economic rationale for the Chinese healthcare system to consider ADCHM as the first-line treatment option for ES-SCLC and the post-marketing pricing of adebrelimab.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Author contributions

Study design and supervision: MY, YH; data analysis and interpretation: QW, WZ; data collection: YH, RC; manuscript writing: MY; final approval of the manuscript: All authors.

Funding

This study was supported in Social Development Project of Fuzhou Science and Technology Department (Grant number: 2021-S-108); Startup Fund for scientific research, Fujian Medical University (Grant number: 2019QH1301; 2021QH1203); Mindong Hospital Science Fund (Grant number: 2022YN005). This study was not supported by any pharmaceutical company.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1019826/full#supplementary-material

References

Ding, D., Hu, H., Li, S., Zhu, Y., Shi, Y., Liao, M., et al. (2021). Cost-effectiveness analysis of durvalumab plus chemotherapy in the first-line treatment of extensive-stage small cell lung cancer. *J. Natl. Compr. Canc. Netw.* 19, 1141–1147. doi:10.6004/jnccn.2020.7796

Goulart, B., and Ramsey, S. (2011). A trial-based assessment of the cost-utility of bevacizumab and chemotherapy versus chemotherapy alone for advanced non-small cell lung cancer. *Value Health* 14, 836–845. doi:10.1016/j.jval.2011.04.004

Horn, L., Mansfield, A. S., Szczęsna, A., Havel, L., Krzakowski, M., Hochmair, M. J., et al. (2018). First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N. Engl. J. Med.* 379, 2220–2229. doi:10.1056/NEJMoa1809064

Hoyle, M., Green, C., Thompson-Coon, J., Liu, Z., Welch, K., Moxham, T., et al. (2010). Cost-effectiveness of temsirolimus for first line treatment of advanced renal cell carcinoma. *Value Health* 13, 61–68. doi:10.1111/j.1524-4733.2009.00617.x

Hoyle, M. W., and Henley, W. (2011). Improved curve fits to summary survival data: Application to economic evaluation of health technologies. *BMC Med. Res. Methodol.* 11, 139. doi:10.1186/1471-2288-11-139

Husereau, D., Drummond, M., Augustovski, F., de Bekker-Grob, E., Briggs, A. H., Carswell, C., et al. (2022). Consolidated health economic evaluation

reporting standards 2022 (CHEERS 2022) statement: Updated reporting guidance for health economic evaluations. *Value Health.* 25, 3–9. doi:10.1016/j.jval.2021.11.1351

Ishak, K. J., Kreif, N., Benedict, A., and Muszbek, N. (2013). Overview of parametric survival analysis for health-economic applications. *Pharmacoeconomics* 31, 663–675. doi:10.1007/s40273-013-0064-3

Kang, S., Wang, X., Zhang, Y., Zhang, B., Shang, F., and Guo, W. (2021). First-line treatments for extensive-stage small-cell lung cancer with immune checkpoint inhibitors plus chemotherapy: A network meta-analysis and cost-effectiveness analysis. *Front. Oncol.* 11, 740091. doi:10.3389/fonc.2021.740091

Karachaliou, N., Pilotto, S., Lazzari, C., Bria, E., de Marinis, F., and Rosell, R. (2016). Cellular and molecular biology of small cell lung cancer: An overview. *Transl. Lung Cancer Res.* 5, 2–15. doi:10.3978/j.issn.2218-6751.2016.01.02

Li, J. B., Lin, Z. C., Wong, M., Wang, H., Li, M., and Li, S. (2022). A cost-effectiveness analysis of capecitabine maintenance therapy versus routine follow-up for early-stage triple-negative breast cancer patients after standard treatment from a perspective of Chinese society. *BMC Med.* 20, 320. doi:10.1186/s12916-022-02516-9

Li, L. Y., Wang, H., Chen, X., Li, W. Q., and Cui, J. W. (2019). First-line atezolizumab plus chemotherapy in treatment of extensive small cell lung cancer: A cost-effectiveness analysis from China. *Chin. Med. J.* 132, 2790–2794. doi:10.1097/CM9.0000000000000536

Li, M., Lin, S., Wilson, L., Huang, P., Wang, H., Lai, S., et al. (2021). Cost-effectiveness analysis of hepatic arterial infusion of FOLFOX combined sorafenib for advanced hepatocellular carcinoma with portal vein invasion. *Front. Oncol.* 11, 562135. doi:10.3389/fonc.2021.562135

Lin, S., Luo, S., Gu, D., Li, M., Rao, X., Wang, C., et al. (2021). First-line durvalumab in addition to etoposide and platinum for extensive-stage small cell lung cancer: A U.S.-Based cost-effectiveness analysis. *Oncologist* 26, e2013–e2020. doi:10.1002/onco.13954

Liu, G., and Kang, S. (2022). Cost-effectiveness of adding durvalumab to first-line chemotherapy for extensive-stage small-cell lung cancer in China. *Expert Rev. pharmacoecon. Outcomes Res.* 22, 85–91. doi:10.1080/14737167.2021.1888717

Liu, H. S., Wu J, W. J., and Yang, L. L. H. J. (2011). China guidelines for pharmacoeconomic evaluations pharmaceutical economics. *China J. Pharmaceut. Econ.*, 3, 6-9+11-48.

Liu, Q., Luo, X., Yi, L., Zeng, X., and Tan, C. (2021a). First-line chemo-immunotherapy for extensive-stage small-cell lung cancer: A United States-based cost-effectiveness analysis. *Front. Oncol.* 11, 699781. doi:10.3389/fonc.2021.699781

Liu, Q., Tan, C., Yi, L., Wan, X., Peng, L., Li, J., et al. (2021b). Cost-effectiveness analysis of pembrolizumab plus chemotherapy as first-line therapy for extensive-stage small-cell lung cancer. *PLoS ONE* 16, e0258605. doi:10.1371/journal.pone.0258605

Liu, Y., Hu, X., Jiang, J., Yang, L., Zhou, S., Liu, P., et al. (2020). A prospective study of apatinib in patients with extensive-stage small cell lung cancer after failure of two or more lines of chemotherapy. *Oncologist* 25, e833–e842. doi:10.1634/theoncologist.2019-0391

Nafees, B., Lloyd, A. J., Dewilde, S., Rajan, N., and Lorenzo, M. (2017). Health state utilities in non-small cell lung cancer: An international study. *Asia. Pac. J. Clin. Oncol.* 13, e195–e203. doi:10.1111/ajco.12477

National Bureau of Statistics (2021). China statistical yearbook. Available at: http://www.stats.gov.cn/tjsj/ndsj/2021/indexch.htm (Accessed Aug 1, 2022).

Oronsky, B., Abrouk, N., Caroen, S., Lybeck, M., Guo, X., Wang, X., et al. (2022). A 2022 update on extensive stage small-cell lung cancer (SCLC). *J. Cancer* 13, 2945–2953. doi:10.7150/jca.75622

Oronsky, B., Reid, T. R., Oronsky, A., and Carter, C. A. (2017). What's new in SCLC? A review. *Neoplasia* 19, 842–847. doi:10.1016/j.neo.2017.07.007

Paz-Ares, L., Dvorkin, M., Chen, Y., Reinmuth, N., Hotta, K., Trukhin, D., et al. (2019). Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): A randomised, controlled, open-label, phase 3 trial. *Lancet* 394, 1929–1939. doi:10.1016/S0140-6736(19)32222-6

Peng, Y., Zeng, X., Peng, L., Liu, Q., Yi, L., Luo, X., et al. (2022). Sintilimab plus bevacizumab biosimilar versus sorafenib as first-line treatment for unresectable hepatocellular carcinoma: A cost-effectiveness analysis. *Front. Pharmacol.* 13, 778505. doi:10.3389/fphar.2022.778505

Rudin, C. M., Awad, M. M., Navarro, A., Gottfried, M., Peters, S., Csőszi, T., et al. (2020). Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: Randomized, double-blind, phase III KEYNOTE-604 study. *J. Clin. Oncol.* 38, 2369–2379. doi:10.1200/JCO.20.00793

Rudin, C. M., Brambilla, E., Faivre-Finn, C., and Sage, J. (2021). Small-cell lung cancer. *Nat. Rev. Dis. Prim.* 7, 3. doi:10.1038/s41572-020-00235-0

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021). Global cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *Ca. Cancer J. Clin.* 71, 209–249. doi:10.3322/caac.21660

The General Office of the National Health and Health Commission (2022). Notice of the general Office of the national health and health commission on printing distributing the guidelines for the treatment of Oncology and hematology-related diseases. Available at: http://www.nhc.gov.cn/yzygj/s2911/202204/a0e67177df1f439898683e1333957c74.shtml (accessed Aug 1, 2022).

Tong, Y. H., Ding, H. Y., Xin, W. X., Zhong, L. K., Xu, G. Q., Zhang, B., et al. (2022). Cost-effectiveness analysis of durvalumab plus etoposide: Platinum in the first-line therapy of extensive stage small-cell lung cancer from the Chinese payers' perspective. *Tumori* 108, 33–39. doi:10.1177/0300891620985309

Wan, X., Zhang, Y., Tan, C., Zeng, X., and Peng, L. (2019). First-line nivolumab plus ipilimumab vs sunitinib for metastatic renal cell carcinoma: A cost-effectiveness analysis. *JAMA Oncol.* 5, 491–496. doi:10.1001/jamaoncol.2018.7086

Wang, J., Zhou, C., Yao, W., Wang, Q., Min, X., Chen, G., et al. (2022). Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 23, 739–747. doi:10.1016/S1470-2045(22)00224-8

Wang, Y., Rui, M., Yang, L., Wang, X., Shang, Y., Ma, A., et al. (2021). Economic evaluation of first-line atezolizumab for extensive-stage small-cell lung cancer in the US. *Front. Public Health* 9, 650392. doi:10.3389/fpubh.2021.650392

Williams, C., Lewsey, J. D., Mackay, D. F., and Briggs, A. H. (2017). Estimation of survival probabilities for use in cost-effectiveness analyses: A comparison of a multi-state modeling survival analysis approach with partitioned survival and Markov decision-analytic modeling. *Med. Decis. Mak.* 37, 427–439. doi:10.1177/0272989X16670617

Yaozhi Net (2022). Drugdataexpy: Marketing information, local bid-wining price. Available at: https://data.yaozh.com (Accessed Aug 1, 2022).

Zhang, Q., Wu, P., He, X., Ding, Y., and Shu, Y. (2021). Cost-effectiveness analysis of camrelizumab vs. Placebo added to chemotherapy as first-line therapy for advanced or metastatic esophageal squamous cell carcinoma in China. *Front. Oncol.* 11, 790373. doi:10.3389/fonc.2021.790373

Zhang, L, L., Hang, Y., Liu, M., Li, N., and Cai, H. (2020). First-line durvalumab plus platinum-etoposide versus platinum-etoposide for extensive-stage small-cell lung cancer: A cost-effectiveness analysis. *Front. Oncol.* 10, 602185. doi:10.3389/fonc.2020.602185

Zhang, P. F, P. F., Xie, D., and Li, Q. (2020). Cost-effectiveness analysis of nivolumab in the second-line treatment for advanced esophageal squamous cell carcinoma. *Future Oncol.* 16, 1189–1198. doi:10.2217/fon-2019-0821

Zhao, Y., Wan, B., Zhang, T., Xu, Y., Liu, H., Lv, T., et al. (2019). Irinotecan, topotecan, paclitaxel or docetaxel for second-line treatment of small cell lung cancer: A single-center retrospective study of efficiency comparation and prognosis analysis. *Transl. Lung Cancer Res.* 8, 829–837. doi:10.21037/tlcr.2019.10.21

Zhou, K., Zhou, J., Huang, J., Zhang, N., Bai, L., Yang, Y., et al. (2019). Cost-effectiveness analysis of atezolizumab plus chemotherapy in the first-line treatment of extensive-stage small-cell lung cancer. *Lung Cancer* 130, 1–4. doi:10.1016/j.lungcan.2019.01.019

Zhu, J., He, W., Ye, M., Fu, J., Chu, Y. B., Zhao, Y. Y., et al. (2018). Cost-effectiveness of afatinib and erlotinib as second-line treatments for advanced squamous cell carcinoma of the lung. *Future Oncol.* 14, 2833–2840. doi:10.2217/fon-2018-0321

Zhu, Y., Hu, H., Ding, D., Li, S., Liao, M., Shi, Y., et al. (2021). First-line pembrolizumab plus chemotherapy for extensive-stage small-cell lung cancer: A United States-based cost-effectiveness analysis. *Cost. Eff. Resour. Alloc.* 19, 77. doi:10.1186/s12962-021-00329-w

frontiers | Frontiers in Pharmacology

TYPE Systematic Review
PUBLISHED 05 December 2022
DOI 10.3389/fphar.2022.1025326

OPEN ACCESS

EDITED BY
Carlos Alves,
University of Coimbra, Portugal

REVIEWED BY
Joaquín Sáez Peñataro,
Hospital Clinic of Barcelona, Spain
Filipa Sampaio,
Uppsala University, Sweden

*CORRESPONDENCE
Meryl Darlington,
meryl.darlington@aphp.fr

SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 22 August 2022
ACCEPTED 31 October 2022
PUBLISHED 05 December 2022

CITATION
Darlington M, Scarica R, Chavez-Pacheco X, Blamplain Segar L and Durand-Zaleski I (2022), Decrementally cost-effective health technologies in non-inferiority studies: A systematic review.
Front. Pharmacol. 13:1025326.
doi: 10.3389/fphar.2022.1025326

Decrementally cost-effective health technologies in non-inferiority studies: A systematic review

Meryl Darlington[1]*, Raffaele Scarica[1], Xyomara Chavez-Pacheco[1], Laeticia Blamplain Segar[1] and Isabelle Durand-Zaleski[1,2]

[1]Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Hôtel Dieu, Clinical Research Unit Eco Ile de France, Paris, France, [2]Université de Paris Est Creteil INSERM UMRS, Paris, France

Background: HTA guidance has generally been driven by situations where innovative and usually more expensive technologies are compared to the prevailing standards of care. Cheaper and less efficacious interventions have received scarce attention, although strategies with minimal individual efficacy losses might produce collective health gains when savings are redistributed.

Purpose: This systematic review of health economic evaluations identified interventions that are both cost and outcome reducing to procure a list of candidate decrementally cost-effective technologies.

Data Sources: English language searches were performed in PubMed, EMBASE and ClinicalTrials.gov covering 2005 to September 2021.

Study Selection: Full economic evaluations reporting in English decrementally cost-effective health technologies based on RCT data, modelling or mixed methods.

Data Synthesis: After filtering 4,975 studies found through the systematic database search, 107 decrementally cost-effective health technologies (HTs) were identified. Nearly a third were services (n = 29) and similarly for drugs (n = 31). For over half of the studies (n = 54) health outcomes were measured in QALYs and the cost-utility ratios varied from €140 to €5 million saved per QALY lost, albeit with time horizons varying from 4 days of follow-up to lifetime extrapolations. Less than a quarter of the studies were carried out from the societal perspective.

Limitations: Despite including ClinicalTrials.gov as data source, unpublished studies may have been missed.

Conclusions: Our results show a growth in recent years in the number of economic publications demonstrating decrementally cost-effective HTs. Economic tools are needed to facilitate the adoption of such HTs by policy-makers at the national level to maximise health outcomes at the population level.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=95504, identifier CRD42018095504.

KEYWORDS

systematic review, cost, economics, non-inferiority, health technology assessment

Introduction

Since the 1970s Health Technology Assessments (HTAs) have been increasingly used to evaluate the efficacy and costs of Health Technologies (HTs). Against a background of increasing demands on limited resources, HTAs have a growing impact on health policy. The typical situations met in HTA consist of incremental innovations that are characterised by cost increases and efficacy enhancements compared to usual standards of care. These innovations belong to the north-east quadrant of the cost-effectiveness (C-E) plane (Black, 1990). The north-east quadrant implies trade-offs on how much society is willing to pay for the extra efficacy, the theoretical and empirical foundations of priority setting, pricing and reimbursement decisions nearly always relate to this quadrant. The south-west quadrant (lower cost/lower efficacy) has been given even less consideration; a review of published C-E analyses reported that only 2% of C-E studies were for interventions associated with lower cost and lower efficacy (Nelson et al., 2009). In settings where resources are limited, the adoption of cost-reducing technologies may lead to budget reallocation in order to improve health outcomes in other domains even if they lead to slightly worse individual outcomes in a specific disease or patient subgroup. Nonetheless, in Europe the development and diffusion of better medical interventions are more common, given that clinical research stakeholders are mostly encouraged to investigate the improvement of care quality, or at least to demonstrate equal care quality (Kent et al., 2004).

However, in the last decade, non-inferiority trials have gained attention among health stakeholders. In these trials, an alternative treatment has an efficacy similar to, or at least not much worse than, the standard treatment, with possible advantages regarding safety, convenience, better compliance, or cost reduction. A search of the Cochrane Controlled Trials Register for two periods of 10 years (1999–2009 and 2009–2019) demonstrated that the total number of trials registered worldwide increased threefold (from 0.3 million to over one million) whilst the number of non-inferiority or equivalence trials increased fourfold (from 6 K to 29 K). Currently, there is no guidance on decision-making for decrementally cost-effective (d-CE) interventions (health technologies associated with a cost and efficacy reduction profile that is deemed acceptable) and the reticence in accepting a small loss in quality-adjusted life years (QALYs) has not been accommodated in routine reimbursement decisions. The definition of a non-inferiority margin is based on both statistical reasoning and clinical judgment, under the assumption that the difference (decrease) in effect will not be harmful to patients. The concept of applying a non-inferiority margin to economic evaluations has been explored for model-based studies and requires the intervention to be cost-saving, non-inferior for the clinical outcome and also non-inferior for the quality of life dimension as measured by QALYs. However it is unusual to estimate non-inferiority margins for QALYs (Xie et al., 2019). Non-inferiority studies provide good material for economic evaluations which study the joint distribution of costs and outcome and represent uncertainty on the cost-effectiveness plane or through the use of the net-benefit statistic (Briggs and O'Brien, 2001). In some cases, the trade-offs associated with implementing d-CE strategies have been measured, yet no policy decisions have been systematically implemented. (Dowie et al., 2015).

The objective of this systematic review was to identify d-CE studies published recently in order to inform researchers and decision-makers about the d-CE technologies currently available.

Materials and methods

This review was conducted in accordance with the five-step approach for systematic review of economic evaluations published in the "Expert Review of Pharmacoeconomics and Outcomes Research" journal (Thielen et al., 2016) (van Mastrigt et al., 2016) (Wijnen et al., 2016). The protocol was published on PROSPERO (Registration number: CRD42018095504) and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (Moher et al., 2009).

Data sources and searches

Systematic electronic searches were conducted using PubMed, EMBASE and the Clinical Trials registry (https://clinicaltrials.gov/). Other databases were investigated with non-systematic searches such as Tufts, EuroCT, EBSCOhost, CRD York and ISRCTN as well as grey literature, published between 1st January 2005 and 4th October 2021. Manual searches were carried out using a

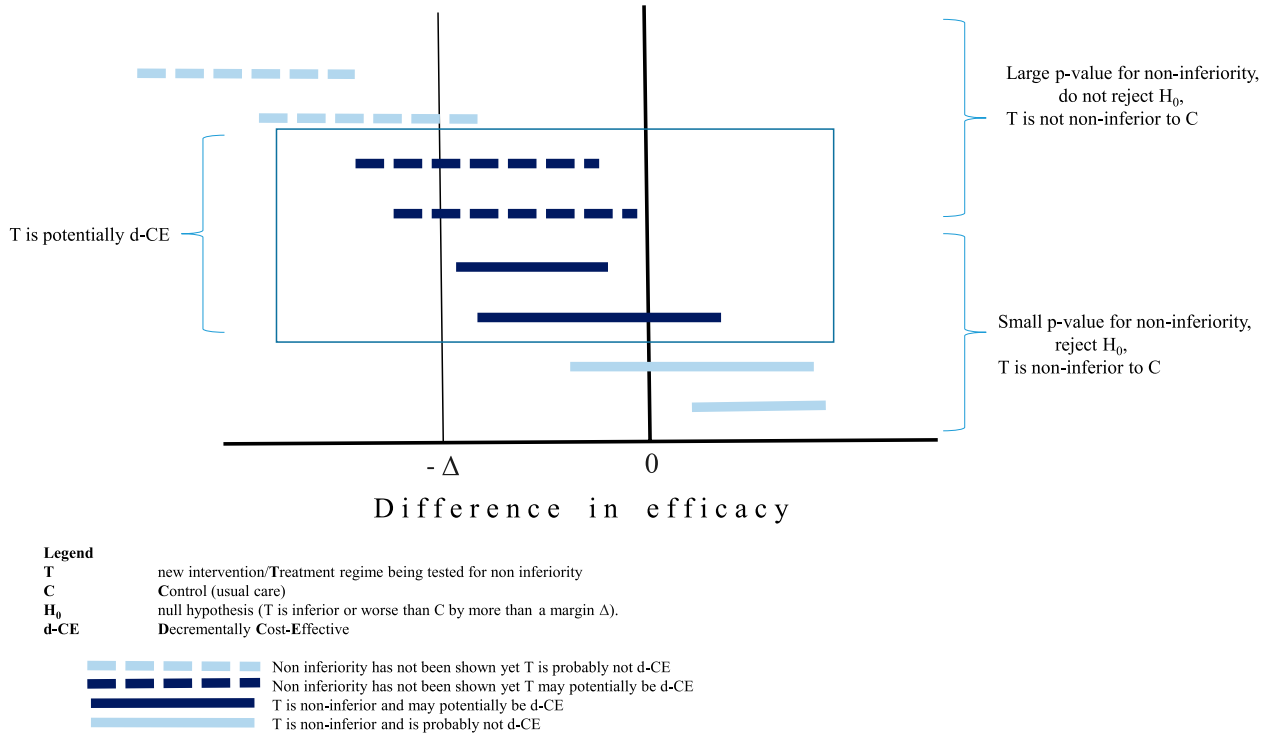

FIGURE 1
Non-inferiority studies and decremental cost-effectiveness.

snowballing technique and investigating citations found in pertinent articles. Full search strategies are provided in the Supplementary Appendix S1.

Study selection

The inclusion criteria, that studies should demonstrate decremental C-E, would normally require definition of a threshold related to the willingness to accept (WTA) a loss in QALY for monetary gain. However, the efficacy in C-E studies can be measured in natural units (e.g., mmHg for blood pressure, HbA1c for diabetes) or in health utilities (QALY, Disability-adjusted life years, or other). Given that our review covers multiple countries having different criteria for evaluating C-E and that we included studies with efficacy measured in natural units, we did not use a threshold to determine inclusion or exclusion of a study. When the decremental C-E ratio (d-CER) was calculated and a C-E plane used to show the uncertainty around these results, we were able to identify that the cloud of points fell at least 50% in the south-west quadrant. Where this information was not available in the article, we checked the confidence intervals of the disaggregated data (costs and efficacy) to estimate that a cloud would almost certainly be at least 50% in the south-west quadrant.

Whilst this review focussed on technologies with a very strong economic rationale for implementation balanced by a weak medical rational, such as the non-inferior medical efficacy, when a health technology is found to be non-inferior to the comparator, the HT is not necessarily decrementally cost-effective as shown in Figure 1. The bottom four horizontal lines represent non-inferior technologies compared to usual care. Even in the event that the economic evaluation demonstrates large potential cost savings, two of these four (the two closest to the x axis) would not result in a d-CER since these technologies are actually superior to usual care. The top four horizontal lines results have not been shown to be non-inferior, yet there is a possibility that a C-E ratio for two of the examples shown could be of interest given that the point value is within the non-inferiority margin and the confidence intervals are right skewed from the margin value (as shown by Δ). Whilst from a clinical point of view, the classic rules of inference based on using the p-value to demonstrate significance of (in this case) non-inferiority are still applied, these are arbitrary rules and not relevant to the decisions which are informed by health economic evaluations (Claxton, 1999).

The search was conducted according to the following inclusion criteria: 1) the interventions were applied to human subjects; 2) the interventions were evaluated in a

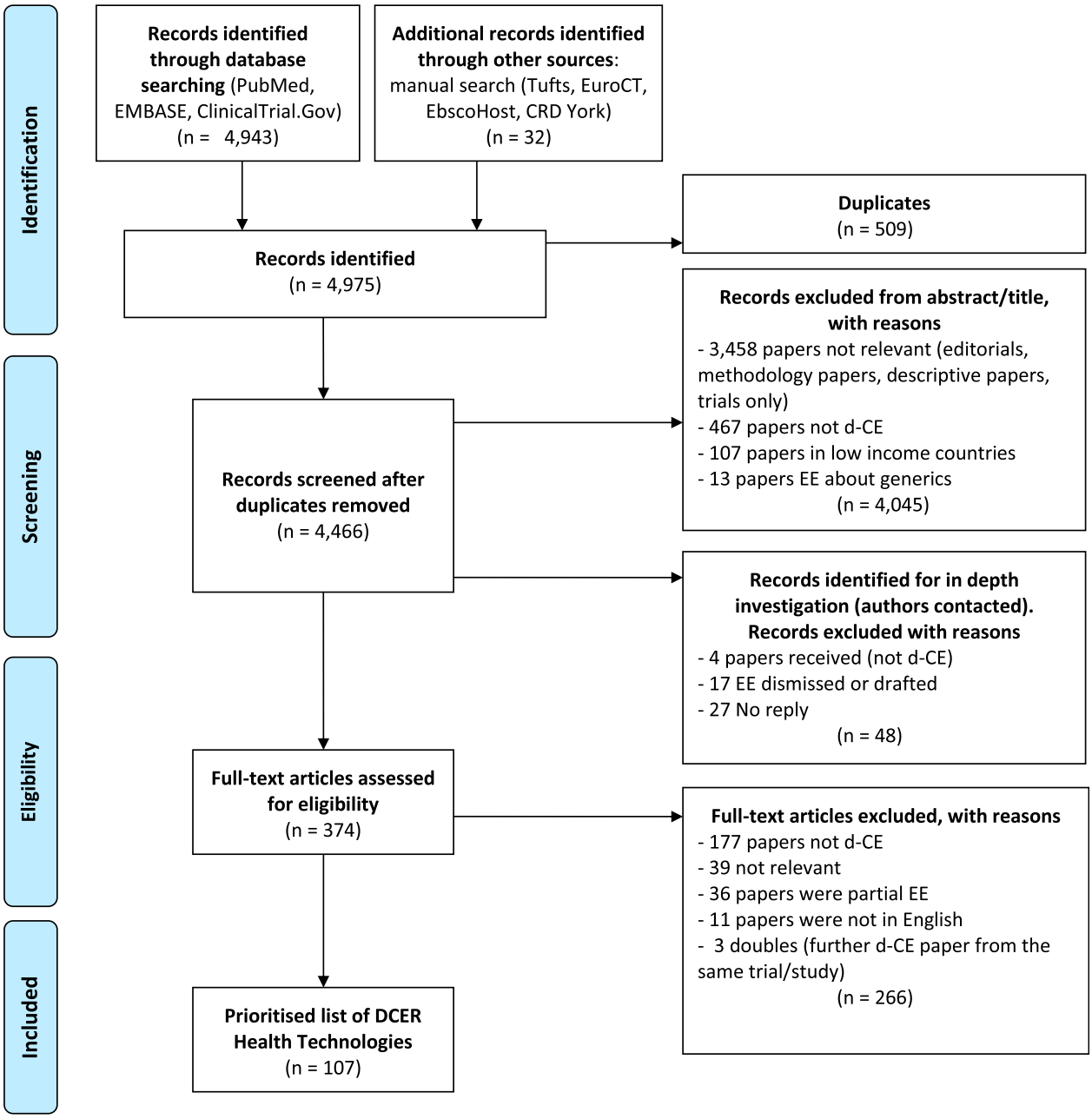

FIGURE 2
PRISMA flowchart of study selection.

full economic evaluation as defined in Drummond et al. (Drummond and Jefferson, 1996) thus comparing at least two HTs with assessment of both costs and outcomes; 3) the interventions were evaluated in countries defined as an upper-middle-income or high-income economy according to the World Bank's 2018 country classification by income level; 4) the interventions were traditional HTs according to the WHO definition: "the application of organized knowledge and skills in the form of medicines, medical devices, vaccines, procedures and systems developed to solve a health problem and improve quality of life"; 5) the interventions should be d-CE compared to the standard of care; 6) studies should be written in English.

Publications reporting on methodological issues, discussion articles, partial economic evaluations, HT including a generic component, comment letters and editorials were excluded. We

excluded duplicates found in more than one database. The reasons for exclusion for each study were reported on a PRISMA flowchart (Figure 2). Studies comparing generic drugs to the commercial variety were excluded from the review. Biosimilar products, that are not identical to the original branded biologic and that must have their own clinical data and pharmacovigilance, were included. We carried out a systematic search of trials as well as protocols characterised as equivalence or non-inferiority results and for which an economic analysis was planned.

Data extraction and quality assessment

The results of the search strategy in PubMed, Embase and ClincialTrials.gov were exported and managed in Excel files and Rayyan QCRI (https://rayyan.qcri.org/). Study selection was based on the inclusion and exclusion criteria and was carried out in double. Two reviewers (XC and RS) independently screened titles and abstracts using the inclusion criteria. Secondly, the full-text version was screened in double by three reviewers (XC, LBS, RS) and a final decision made with respect to the inclusion/exclusion criteria. Any disagreement or conflicting views between the reviewers over the eligibility of specific economic evaluations was resolved by discussion or the final judgment of a fourth reviewer (MD). Both stages of the selection process were piloted and if necessary modified. Studies found through trial registry records or published protocols were considered for in-depth investigations when the clinical non-inferior or equivalence results were published and an economic evaluation was planned for these trials. Internet searches were conducted to ascertain if any economic results had been published and in case of inconclusive findings, investigators were contacted to determine if an economic evaluation had been carried out or why the economic results had not been diffused.

We reviewed four checklists for quality assessment: Drummond Checklist (Drummond and Jefferson, 1996), Philips checklist (Philips et al., 2006), CHEERS checklist (Husereau et al., 2013) and the CHEC list (Evers et al., 2005), one for bias (Adarkwah et al., 2016) and three for transferability (Drummond et al., 2009) (Wijnen et al., 2016) (Welte et al., 2004). The three components of quality, bias and transferability had a certain amount of overlap in the questions and we collated the questions and eliminated redundancy from the different sources to create a reduced list shown in Supplementary Materials Appendix 3. The final list used for screening full text articles had 22 questions. In order to calculate a quality score, a value of 1, 0.5, 0 or not applicable (NA) was given to each question. A score of 1 indicated that the reviewer considered that the article fully satisfied the question. A score of 0 indicated that the paper did not satisfy the criteria at all. The score of 0.5 was awarded when it seems that some attempt had been made to address the question but that it was not completely adequate. The option NA was selected in cases where it was not appropriate to answer the question. For example, if the time horizon was 1 year or less then discounting would not be carried out and NA was coded for this question (item 10 on the checklist). The overall score of the paper was the sum of the score for each question divided by the number of applicable questions.

Data synthesis and analysis

Publication information, study characteristics and findings from the included studies, related to the research question, were gathered in a database form using Excel. The data extraction list from Wijnen et al. (Wijnen et al., 2016) was used as a basis and other items were included that are directly related to non-inferiority or equivalence trials such as study analysis approach of intention to treat *versus* per protocol. When the d-CER was not reported, it was calculated where possible by dividing the differential cost and the differential effect (QALY, Life Years, other) found in the text. Given the different locations, years of study and country-specific elements such as different currencies, the costs were converted into a common currency and price year using the CCEMG—EPPI-Centre Cost Converter as recommended in the five step methodology, which enable us to convert and adjust the d-CER of each article to 2022 euros (€) (https://eppi.ioe.ac.uk/costconversion/).

Results

In total, 4,975 records were found from PubMed, EMBASE, ClinicalTrials.gov and the manual searches. The latter included the results retrieved by using the snowballing technique among the rest of databases such as Tufts, EuroCT, EBSCOhost, CRD York and ISRCTN. After filtering studies according to the inclusion criteria, we found 107 published d-CE economic evaluations, representing 107 days-CE HTs as shown in the PRISMA flowchart (Figure 2). The scope of the articles varied considerably and not all of the published economic evaluations reported the d-CER; when it was not possible to be calculated, the information was shown in disaggregated form. The full list of included studies with key characteristics is available in the supplementary material (appendix 2). Nearly 30% of the 107 HTs were services (n = 29) and similarly for drugs (n = 31). These papers, that were predominantly about cancer, cardiovascular diseases, musculoskeletal disorders and respiratory diseases, were almost equally split between new/alternative technologies (n = 54) and strategies that were using the same technology (n = 53) such as drug tapering studies. Over half of the studies were publicly funded (n = 67) and were primarily carried out in the USA (n = 28) and the UK (n = 23) which reflects the importance and quantity of economic

TABLE 1 Key characteristics of studies with a point estimate of the cost utility ratio greater than €100,000/Qaly lost.

Author	Year/ country		Disease	Intervention	Type	Effects and time horizon		DCER 2022 €
Bansback et al. (2017)	2017	US	Rheumatoid arthritis	Triple Therapy	RCT	-0.016 QALY	48 weeks	€ 897 558/ QALY Lost
Blondon et al. (2020)	2020	US	Pulmonary embolism	Age-adjusted cutoff	Decision Model	- 0.0001 QALYs	Lifetime	€188 361/ QALYs lost
Brown et al. (2018)	2018	UK	Rheumatoid arthritis	Etanercept/Adalimumab	Mixed	-0.02 QALY	2 years	€ 242 916/ QALY Lost
Clark et al. (2015)	2015	UK	Abnormal uterine bleeding	Outpatient	RCT	-0.006 QALYs	1 year	€ 206 490/ QALY Lost
Corral et al. (2017)	2017	Spain	Obstructive sleep apnoea	HRP Home respiratory polygraphy	RCT	-0.004 QALYs	6 months	€ 144 555/ QALY Lost
Cram et al. (2006)	2006	US	Cardiac Arrest	Automated external defibrillators (AEDs)	Decision Model	-0.85 QALYs	Lifetime	€ 125 018/ QALY Lost
Cross et al. (2010)	2010	UK	COPD	Manual chest physiotherapy	RCT	- 0.001 QALYs	6 months	€605 380/ QALY lost
Dakin et al. (2014)	2014	UK	Neovascular age-related macular degeneration (nAMD)	Continuous Bevacizumab	RCT	-0.004 QALY	2 years	€ 5 185 700/ QALY Lost
Dickson et al. (2011)	2011	UK	Lung Cancer	Erlotinib	Mixed	-0.1007 QALYs	Life-time	€123 809/ QALY lost
Ferket et al. (2017)	2017	US	Osteoarthritis	TKR <35 SF PCS	Mixed	-0.008 QALY	Life-time	€ 799 548/ QALY Lost
van den Houten et al. (2016)	2016	Netherl	Intermittent claudication	Endovascular revascularization (ER)	Markov	–0.07 QALYs	5 years	€ 106 140/ QALY Lost
Howard et al. (2017)	2017	UK	Leukaemia	FCM-miniR	Mixed	-0.059 QALYs	Life-time	€ 147 765/ QALY Lost
Kievit et al. (2016)	2016	Netherl	Rheumatoid arthritis	Dose optimisation	RCT	–0.02 QALYs	18 months	€ 681 444/ QALY Lost
Ladabaum et al. (2020)	2020	UK	Colorectal cancer	Tailored colonoscopy	Decision Model	- 0,0015 QALYs	Lifetime	€193 353/ QALYs
Latimer et al. (2013)	2013	UK	Hospital Falls	New Flooring	Mixed	-0.006 QALY	Life-time	€ 198 120/ QALY Lost
Mahmoud et al. (2021)	2021	Netherl	Ulcerative colitis	Withdrawal of anti-tumour necrosis factor alpha (TNF)	Markov	-0,04 QALYs	5 years	€ 318 434,85/ QALY
Manca et al. (2006)	2006	UK	Neck pain	Brief physiotherapy intervention	RCT	-0.0010 QALY	12 months	€ 116 310/ QALY Lost
Navarro et al. (2020)	2020	Spain	Rheumatoid arthritis (RA)	tofacitinib-containing treatment sequences	RCT	– 0.092 QALY	Lifetime	€440 918/ QALY
O'Day et al. (2016)	2016	US	Heart Failure	I-mIBG imaging	Decision Model	-0.001 QALYs	2 years	€ 5 044 460/ QALY Lost
Oddershed et al. (2016)	2016	UK	HIV	Protease inhibitor	Mixed	-0.0227 QALYs	3 years	€ 379 295/ QALY Lost
Okeke et al. (2021)	2021	UK	Missed miscarriage	mifepristone and misoprostol (MifeMiso)	RCT	- 0,04% QALYs	21 days	€425 080/ QALY
Shapiro et al. (2017)	2017	US	Breast Cancer	ZA every 3 months	Markov	-0.01 QALYs	2 years	€ 322 672/ QALY Lost
Stoecker et al. (2013)	2013	US	Pneumococcal diseases (vaccination)	2+1 pneumococcal vaccine	Prob. Model	-0.005 QALYs	Life-time	€ 285 351/ QALY
Thoma et al. (2014)	2014	Canada	Breast Mammaplasty	Vertical Scar Reduction	RCT	–0.01 QALY	1 year	€783 556/ QALY Lost
Udkoff and Eichenfield. (2017)	2017	US	Psoriasis	Ixekizumab every 4 weeks	Markov	-0.006 QALYs	5 years	€ 3 138 538/ QALY Lost
Wagmiller et al. (2006)	2006	US	Prostate cancer	Individualized schedule	Model	-0.005 QALY	5 years	€ 782 954/ QALY Lost
Wailoo et al. (2008)	2008	US	Rheumatoid arthritis	Anakinra	Decision Model	-0.2 QALYs	Life-time	€ 231 773/ QALY Lost
Wong et al. (2015)	2015	China	Transitional care	Home visit	RCT	–0.0002 QALYs	28 days	€ 1 175 700/ QALY Lost

studies in general carried out in those countries. Over half of the economic evaluations were conducted alongside randomised control trials (n = 65).

For the studies where it was possible to calculate the decremental cost-utility ratio, it ranged from €151 to €5,044,460 saved per QALY lost. Table 1 shows the key characteristics of interventions with a point estimate of the cost utility ratio above €100,000 saved per QALY lost. The time horizons varied from 4 days to lifetime extrapolations in the case of modelling studies. For over half of the studies (n = 54) health outcomes were expressed in QALYs, in other cases effectiveness was measured in natural units or functional scales.

In total, 78% of the studies evaluated had high or very high quality, bias and transferability scores. Over 90% of the studies included in this review clearly stated their objectives and population characteristics. Only 28 of the economic analyses were carried out from the societal perspective and this typically meant an estimation of productivity costs in terms of absenteeism from work and cost of caregiving. The costs estimated rarely included out of pocket payments or private health insurance payments that can be important in some countries despite universal coverage and social health insurance. Generalisability of the results to other settings were discussed in 73% of papers and ethical and distributional issues were only addressed in two-thirds of papers. For 25% papers no sponsorship information was communicated.

The expanded search to conference abstracts, posters, published protocols and ClinicalTrials.gov registry entries for equivalence or non-inferiority trials, a total of 48 records were identified for in depth investigation and the first authors were contacted to investigate if an economic evaluation had been published. Only 21 replies were received and of these just four studies had a publication available, which were not d-CE.

Discussion

This review aimed to summarise the existing economic studies of decrementally cost-effective technologies published since 2005. Given its international nature and the variety of effectiveness endpoints, no threshold was used to characterise whether costs savings associated with a loss of health were acceptable or not. However, it is under debate whether or not the willingness to pay (WTP) value would be the same as the willingness to accept value. The societal point of view indicates that WTA is usually higher than WTP, potentially with double the cost difference for one QALY lost than the WTP for one QALY gained (Kievit et al., 2016). The net monetary benefit approach has been advocated, however it still requires a decision on the acceptable loss of efficacy for the non-inferiority condition to be met, as well as scenarios on the decision maker's willingness to accept thresholds (Xie et al., 2019).

The 54 studies which used QALYs as the measure of outcome reported a wide range of d-CERs, from an unacceptable €151 to a high € 5,044,460 saved per QALY lost, with a fair share of them reporting results above €100,000 saved per QALY lost. However, the C-E results of the studies cannot be directly compared due to methodological differences such as the different economic perspectives, different discount rates and different health systems.

In the Netherlands, the WTA is considered to be € 80,000 saved per QALY lost, although this value has not been officially stated and we had applied this threshold value in our review, we would have excluded more than 30% of the papers. A previous systematic review on d-CE HTs, conducted over the time period 2002–2007, identified just eight d-CE interventions (Nelson et al., 2009).

Besides the growth of economic evaluations published in the recent years and the conservative approach of the above-mentioned study only d-CE interventions being at least $100,000 cost saving for each QALY lost were included. However, there could be other reasons for the higher number of studies found in our review. For example, 46 out of 66 RCT-based economic evaluations were based on non-inferiority or equivalence clinical trials and non-inferiority clinical trials are being performed with a greater frequency every year (Murthy et al., 2012). These trials are usually undertaken to test the hypothesis that the new technology will provide better safety at the cost of an acceptable reduction in efficacy. The addition of an economic analysis using QALYs as outcomes in that situation is highly relevant because 1) the new technology can be cost reducing and 2) both safety and efficacy are covered by the generic health related quality of life measure. Moreover, the time period covered by our review included the austerity measures on healthcare spending caused by the global financial crisis which has been a key driver to decision making based on maximising collective health benefits while controlling costs. Curbing overtreatment and rational prescribing is another key topic in healthcare and nearly half of the 107 days-CE HTs we found were dose reduction/de-escalation interventions (OECD and European Union, 2018).

Next steps of research would involve investigating the opportunity cost generated by implementing d-CE HTs in national settings to identify how to displace the financial savings to maximise population's health outcomes. For example, using results from the PIVOT trial, it is has been estimated that switching 45,000 HIV patients in the UK from triple antiretroviral therapy to the clinically non-inferior protease inhibitors monotherapy (until viral load rebound) would lead to cost savings that could be used to generate 22,354 QALYs elsewhere, including 1,486 lives prolonged and 6,735 life-years gained (Oddershede et al., 2016). The potentially collective health gains under limited resources

have also been described in a model by Arbel et al., which has been used by the German health system when comparing alternative interventions under a pre-specified budget constraint (Arbel and Greenberg, 2016) · A less expensive and less effective therapy might add more QALYs in a target population when there are budget constraints (Birch and Gafni, 2004). However, cost saving is rarely the primary reason for choosing a particular treatment strategy. In case of HIV, for example, the WHO rejects the provision of cheaper and less effective treatments in any situation, to avoid the establishment of a double standard of care. It can be argued that it should be mandatory for health professionals to provide the best available option to their patients, but from a broader societal perspective, decision makers may claim that is more important to achieve equity in the supply of medical innovations (Persad and Emanuel, 2017). Since 2010, in OECD countries, the expenditure on health has remained relatively flat within a global context of budget constraint. Policy recommendations for implementing slightly less effective medical interventions, but at significantly lower cost, might represent a more effective use of resources to provide additional health gains to the population (Kent et al., 2004) (OECD and European Union, 2018).

Having identified these 107 days-CE HTs, the question remains for policy makers on which of these could be implemented. Interventions that are highly d-CE for pathologies with a significant burden of disease would probably be most pertinent for investigation by HTA agencies and medical associations. Overcoming the reticence of stakeholders to look into the south-west quadrant of the C-E plan and find consensus for a WTA threshold is a context sensitive issue.

One HT found by this systematic review was based on a RCT that demonstrated that for patients with active rheumatoid arthritis, having failed conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) mono-therapy, triple therapy was non-inferior to the biological disease-modifying anti-rheumatic drugs (bDMARDs) with Methotrexate. The economic analysis estimated an average reduction in QALY of -0.017 and cost savings of $977,805 per QALY lost, mainly attributable to the lower drug costs of csDMARDS (O'Dell et al., 2013) (Bansback et al., 2017). In terms of implementation in Europe, there are different eligibility criteria for reimbursement of bDMARDs depending on the country. For example, in France, where bDMARDs are up to 30 times more expensive than csDMARDs, the eligibility criteria for bDMARD reimbursement do not require minimal disease duration nor that a certain number of csDMARDs fail prior to prescribing a biologic therapy. The percentage of French patients treated with a combination of three csDMARDs was less than 1% in the ESPOIR cohort of 2018. In the UK, where NICE recommends biologics for patients with RA only if the disease activity is severe and has not responded to treatment with a combination of csDMARDs, the National Clinical Audit for RA indicated that at least 46% of English patients received a combination of csDMARDs at some point (HAS, 2019) (Firth et al., 2016). The launch of biosimilar bDMARDs can further affect prescribing habits: the sales of biosimilar Etanercept (Benepali®) increased by 172% in France from 2017 to 2018 (Medic'AM, 2018). However, biosimilars are still relatively expensive compared with csDMARDs and thus triple therapy remains the least costly option in people failing csDMARD monotherapy. Since prescribers do not always follow the HTA guidelines, the question of how to motivate them to do so should be addressed. In addition to reimbursement policy, incentives such as novel payment models to encourage use of a less expensive but much cheaper technologies compared to usual care may be necessary (Hutton et al., 2014).

Despite the increased number of d-CE papers found, it is possible that some studies are not published due to the results being unable to demonstrate non-inferiority, equivalence or in the case of superiority trials, health gains, despite the possibility that an economic evaluation may have unearthed d-CE interventions in some of these cases. A technology that is proven non-inferior (ie possibly inferior but within an acceptable margin for clinical outcome) cannot expect a price premium and will usually be launched at a discounted price (10–15% for example) relative to the comparator. In that sense, policy makers and payers have already answered the question of the equivalence margin for costs, although probably did not consider the joint distribution of costs and effects whether they be clinical outcomes or QALYs. Innovative new frameworks may need to be developed to help policy decisions (Xie et al., 2019).

The comparability of study results was limited by the heterogeneity of endpoints in studies that did not use QALYs, and by the lack of standardization in the selection of non-inferiority margins for clinical trials (Waliszewski et al., 2020). We did not address the ethical process of ensuring that disinvestment decisions are acceptable by the population at large (Pace et al., 2020).

Conclusion

This systematic review has revealed a growth in recent years in the number of economic evaluations of d-CE HTs and identified 107 HTs that are d-CE compared to usual care. Some of these HTs, that represent a potentially large cost saving for a small loss in efficacy, can be examined by decision-makers for uptake in different setting. Economic and policy tools are needed to facilitate the adoption of a decrementally cost-effective health technology in different

settings since this should contribute towards the maximisation of population health outcomes.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

MD and ID-Z prepared the concept and the design of the study; All the authors contributed to the preparation of the material and data collection. The analysis was performed by MD. The first draft of the manuscript was written by MD and ID-Z, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

Funding

This research was funded by the European Union's Horizon 2020 research and innovation programme (H2020) and undertaken under the auspices of IMPACT_HTA (Grant number 779312; http://www.impact-hta.eu).

Acknowledgments

IMPACT HTA guidance implementation Group.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.1025326/full#supplementary-material

References

Adarkwah, C. C., van Gils, P. F., Hiligsmann, M., and Evers, S. M. A. A. (2016). Risk of bias in model-based economic evaluations: The ECOBIAS checklist. *Expert Rev. pharmacoecon. Outcomes Res.* 16, 513–523. doi:10.1586/14737167.2015.1103185

Arbel, R., and Greenberg, D. (2016). Rethinking cost-effectiveness in the era of zero healthcare spending growth. *Int. J. Equity Health* 15, 33. doi:10.1186/s12939-016-0326-8

Bansback, N., Phibbs, C. S., Sun, H., O'Dell, J. R., Brophy, M., Keystone, E. C., et al. (2017). Triple therapy versus biologic therapy for active rheumatoid arthritis: A cost-effectiveness analysis. *Ann. Intern. Med.* 167, 8–16. doi:10.7326/M16-0713

Birch, S., and Gafni, A. (2004). The "NICE" approach to technology assessment: An economics perspective. *Health Care Manag. Sci.* 7, 35–41. doi:10.1023/b:hcms.0000005396.69890.48

Black, W. C. (1990). The CE plane: A graphic representation of cost-effectiveness. *Med. Decis. Mak.* 10, 212–214. doi:10.1177/0272989X9001000308

Blondon, M., Le Gal, G., Meyer, G., Righini, M., and Robert-Ebadi, H. (2020). Age-adjusted D-dimer cutoff for the diagnosis of pulmonary embolism: A cost-effectiveness analysis. *J. Thromb. Haemost.* 18, 865–875. doi:10.1111/jth.14733

Briggs, A. H., and O'Brien, B. J. (2001). The death of cost-minimization analysis? *Health Econ.* 10, 179–184. doi:10.1002/hec.584

Brown, S., Everett, C. C., Naraghi, K., Davies, C., Dawkins, B., Hulme, C., et al. (2018). Alternative tumour necrosis factor inhibitors (TNFi) or abatacept or rituximab following failure of initial TNFi in rheumatoid arthritis: The SWITCH RCT. *Health Technol. Assess.* 22, 1–280. doi:10.3310/hta22340

Clark, T. J., Middleton, L. J., Cooper, N. A., Diwakar, L., Denny, E., Smith, P., et al. (2015). A randomised controlled trial of Outpatient versus inpatient Polyp Treatment (OPT) for abnormal uterine bleeding. *Health Technol. Assess.* 19, 1–194. doi:10.3310/hta19610

Claxton, K. (1999). The irrelevance of inference: A decision-making approach to the stochastic evaluation of health care technologies. *J. Health Econ.* 18, 341–364. doi:10.1016/s0167-6296(98)00039-3

Corral, J., Sánchez-Quiroga, M.-Á., Carmona-Bernal, C., Sánchez-Armengol, Á., de la Torre, A. S., Durán-Cantolla, J., et al. (2017). Conventional polysomnography is not necessary for the management of most patients with suspected obstructive sleep apnea. Noninferiority, randomized controlled trial. *Am. J. Respir. Crit. Care Med.* 196, 1181–1190. doi:10.1164/rccm.201612-2497OC

Cram, P., Katz, D., Vijan, S., Kent, D. M., Langa, K. M., and Fendrick, A. M. (2006). Implantable or external defibrillators for individuals at increased risk of cardiac arrest: Where cost-effectiveness hits fiscal reality. *Value Health* 9, 292–302. doi:10.1111/j.1524-4733.2006.00118.x

Cross, J., Elender, F., Barton, G., Clark, A., Shepstone, L., Blyth, A., et al. (2010). A randomised controlled equivalence trial to determine the effectiveness and cost-utility of manual chest physiotherapy techniques in the management of exacerbations of chronic obstructive pulmonary disease (MATREX). *Health Technol. Assess.* 14, 1–147. doi:10.3310/hta14230

Dakin, H. A., Wordsworth, S., Rogers, C. A., Abangma, G., Raftery, J., Harding, S. P., et al. (2014). Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial. *BMJ Open* 4, e005094. doi:10.1136/bmjopen-2014-005094

Dickson, R., Bagust, A., Boland, A., Blundell, M., Davis, H., Dundar, Y., et al. (2011). Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer after previous platinum-containing chemotherapy: A NICE single technology appraisal. *PharmacoEconomics* 29, 1051–1062. doi:10.2165/11591600-000000000-00000

Dowie, J., Kaltoft, M. K., Nielsen, J. B., and Salkeld, G. (2015). Caveat emptor NICE: Biased use of cost-effectiveness is inefficient and inequitable. *F1000Res.* 4, 1078. doi:10.12688/f1000research.7191.1

Drummond, M., Barbieri, M., Cook, J., Glick, H. A., Lis, J., Malik, F., et al. (2009). Transferability of economic evaluations across jurisdictions: ISPOR good research practices task force report. *Value Health* 12, 409–418. doi:10.1111/j.1524-4733.2008.00489.x

Drummond, M. F., and Jefferson, T. O. (1996). Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 313, 275–283. doi:10.1136/bmj.313.7052.275

Evers, S., Goossens, M., de Vet, H., van Tulder, M., and Ament, A. (2005). Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int. J. Technol. Assess. Health Care* 21, 240–245. doi:10.1017/s0266462305050324

Ferket, B. S., Feldman, Z., Zhou, J., Oei, E. H., Bierma-Zeinstra, S. M. A., and Mazumdar, M. (2017). Impact of total knee replacement practice: Cost effectiveness analysis of data from the osteoarthritis initiative. *BMJ* 356, j1131. doi:10.1136/bmj.j1131

Firth, J., Snowden, N., Ledingham, J., Rivett, A., Galloway, J., Dennison, E., et al. (2016). The first national clinical audit for rheumatoid arthritis. *Br. J. Nurs.* 25, 613–617. doi:10.12968/bjon.2016.25.11.613

HAS (2019). Haute Autorité de Santé - Évaluation médico-économique des traitements de fond biologiques dans la prise en charge de la polyarthrite rhumatoïde. Report.

Howard, D. R., Munir, T., McParland, L., Rawstron, A. C., Chalmers, A., Gregory, W. M., et al. (2017). Clinical effectiveness and cost-effectiveness results from the randomised, phase IIB trial in previously untreated patients with chronic lymphocytic leukaemia to compare fludarabine, cyclophosphamide and rituximab with fludarabine, cyclophosphamide, mitoxantrone and low-dose rituximab: The attenuated dose rituximab with ChemoTherapy in chronic lymphocytic leukaemia (ARCTIC) trial. *Health Technol. Assess.* 21, 1–374. doi:10.3310/hta21280

Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., Greenberg, D., et al. (2013). On behalf of the CHEERS task ForceConsolidated health economic evaluation reporting standards (CHEERS) statement. *BMJ* 346, f1049. doi:10.1136/bmj.f1049

Hutton, D., Newman-Casey, P. A., Tavag, M., Zacks, D., and Stein, J. (2014). Switching to less expensive blindness drug could save medicare Part B $18 billion over A ten-year period. *Health Aff. (Millwood)* 33, 931–939. doi:10.1377/hlthaff.2013.0832

Kent, D. M., Fendrick, A. M., and Langa, K. M. (2004). New and dis-improved: On the evaluation and use of less effective, less expensive medical interventions. *Med. Decis. Mak.* 24, 281–286. doi:10.1177/0272989X04265478

Kievit, W., van Herwaarden, N., van den Hoogen, F. H., van Vollenhoven, R. F., Bijlsma, J. W., van den Bemt, B. J., et al. (2016). Disease activity-guided dose optimisation of adalimumab and etanercept is a cost-effective strategy compared with non-tapering tight control rheumatoid arthritis care: Analyses of the DRESS study. *Ann. Rheum. Dis.* 75, 1939–1944. doi:10.1136/annrheumdis-2015-208317

Ladabaum, U., Mannalithara, A., Mitani, A., and Desai, M. (2020). Clinical and economic impact of tailoring screening to predicted colorectal cancer risk: A decision analytic modeling study. *Cancer Epidemiol. Biomarkers Prev.* 29, 318–328. doi:10.1158/1055-9965.EPI-19-0949

Latimer, N., Dixon, S., Drahota, A. K., and Severs, M. (2013). Cost--utility analysis of a shock-absorbing floor intervention to prevent injuries from falls in hospital wards for older people. *Age Ageing* 42, 641–645. doi:10.1093/ageing/aft076

Mahmoud, R., van Lieshout, C., Frederix, G. W. J., Jharap, B., and Oldenburg, B. (2021). Continuation of anti-TNF in patients with ulcerative colitis in remission is not cost-effective compared with treatment withdrawal: A markov model. *J. Crohns Colitis* 15, 709–718. doi:10.1093/ecco-jcc/jjaa219

Manca, A., Epstein, D. M., Torgerson, D. J., Klaber Moffett, J. A., Coulton, S., Farrin, A. J., et al. (2006). Randomized trial of a brief physiotherapy intervention compared with usual physiotherapy for neck pain patients: Cost-effectiveness analysis. *Int. J. Technol. Assess. Health Care* 22, 67–75. doi:10.1017/s0266462306050859

Medic'AM (2018). ameli.fr - medic'AM. Available At: https://www.ameli.fr/l-assurance-maladie/statistiques-et-publications/donnees-statistiques/medicament/medic-am/medic-am-mensuel-2018.php.

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G.PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* 6, e1000097. doi:10.1371/journal.pmed.1000097

Murthy, V. L., Desai, N. R., Vora, A., and Bhatt, D. L. (2012). Increasing proportion of clinical trials using noninferiority end points. *Clin. Cardiol.* 35, 522–523. doi:10.1002/clc.22040

Navarro, F., Martinez-Sesmero, J. M., Balsa, A., Peral, C., Montoro, M., Valderrama, M., et al. (2020). Cost-effectiveness analysis of treatment sequences containing tofacitinib for the treatment of rheumatoid arthritis in Spain. *Clin. Rheumatol.* 39, 2919–2930. doi:10.1007/s10067-020-05087-3

Nelson, A. L., Cohen, J. T., Greenberg, D., and Kent, D. M. (2009). Much cheaper, almost as good: Decrementally cost-effective medical innovation. *Ann. Intern. Med.* 151, 662–667. doi:10.7326/0003-4819-151-9-200911030-00011

O'Day, K., Levy, W. C., Johnson, M., and Jacobson, A. F. (2016). Cost-effectiveness analysis of iodine-123 meta-iodobenzylguanidine imaging for screening heart failure patients eligible for an implantable cardioverter defibrillator in the USA. *Appl. Health Econ. Health Policy* 14, 361–373. doi:10.1007/s40258-016-0234-5

Oddershede, L., Walker, S., Stöhr, W., Dunn, D. T., Arenas-Pinto, A., Paton, N. I., et al. (2016). Cost effectiveness of protease inhibitor monotherapy versus standard triple therapy in the long-term management of HIV patients: Analysis using evidence from the PIVOT trial. *PharmacoEconomics* 34, 795–804. doi:10.1007/s40273-016-0396-x

O'Dell, J. R., Mikuls, T. R., Taylor, T. H., Ahluwalia, V., Brophy, M., Warren, S. R., et al. (2013). Therapies for active rheumatoid arthritis after methotrexate failure. *N. Engl. J. Med.* 369, 307–318. doi:10.1056/NEJMoa1303006

OECD and European Union (2018). *Health at a Glance: Europe 2018: State of Health in the EU Cycle*. Paris/European Union, Brussels: OECD Publishing. doi:10.1787/health_glance_eur-2018-en

Okeke, C. B., Williams, E. V., Chu, J. J., Devall, A. J., Beeson, L. E., Hardy, P., et al. (2021). Cost-effectiveness of mifepristone and misoprostol versus misoprostol alone for the management of missed miscarriage: An economic evaluation based on the MifeMiso trial. *BJOG Int. J. Obstet. Gynaecol.* 128, 1534–1545. doi:10.1111/1471-0528.16737

Pace, J., Laba, T.-L., Nisingizwe, M.-P., and Lipworth, W. (2020). Formulating an ethics of pharmaceutical disinvestment. *J. Bioeth. Inq.* 17, 75–86. doi:10.1007/s11673-020-09964-z

Persad, G. C., and Emanuel, E. J. (2017). The case for resource sensitivity: Why it is ethical to provide cheaper, less effective treatments in global health. *Hastings Cent. Rep.* 47, 17–24. doi:10.1002/hast.764

Philips, Z., Bojke, L., Sculpher, M., Claxton, K., and Golder, S. (2006). Good practice guidelines for decision-analytic modelling in health technology assessment: A review and consolidation of quality assessment. *PharmacoEconomics* 24, 355–371. doi:10.2165/00019053-200624040-00006

Shapiro, C. L., Moriarty, J. P., Dusetzina, S., Himelstein, A. L., Foster, J. C., Grubbs, S. S., et al. (2017). Cost-effectiveness analysis of monthly zoledronic acid, zoledronic acid every 3 Months, and monthly denosumab in women with breast cancer and skeletal metastases: CALGB 70604 (alliance). *J. Clin. Oncol.* 35, 3949–3955. doi:10.1200/JCO.2017.73.7437

Stoecker, C., Hampton, L. M., Link-Gelles, R., Messonnier, M. L., Zhou, F., and Moore, M. R. (2013). Cost-effectiveness of using 2 vs 3 primary doses of 13-valent pneumococcal conjugate vaccine. *Pediatrics* 132, e324–e332. doi:10.1542/peds.2012-3350

Thielen, F. W., Van Mastrigt, G., Burgers, L. T., Bramer, W. M., Majoie, H., Evers, S., et al. (2016). How to prepare a systematic review of economic evaluations for clinical practice guidelines: Database selection and search strategy development (part 2/3). *Expert Rev. pharmacoecon. Outcomes Res.* 16, 705–721. doi:10.1080/14737167.2016.1246962

Thoma, A., Kaur, M. N., Tsoi, B., Ziolkowski, N., Duku, E., and Goldsmith, C. H. (2014). Cost-effectiveness analysis parallel to a randomized controlled trial comparing vertical scar reduction and inverted T-shaped reduction mammaplasty. *Plast. Reconstr. Surg.* 134, 1093–1107. doi:10.1097/PRS.0000000000000751

Udkoff, J., and Eichenfield, L. F. (2017). Cost-effectiveness analysis of ixekizumab vs etanercept and their manufacturer-recommended dosing regimens in moderate to severe plaque psoriasis. *J. Drugs Dermatol.* 16, 964–970.

van den Houten, M. M. L., Lauret, G. J., Fakhry, F., Fokkenrood, H. J. P., van Asselt, A. D. I., Hunink, M. G. M., et al. (2016). Cost-effectiveness of supervised exercise therapy compared with endovascular revascularization for intermittent claudication. *Br. J. Surg.* 103, 1616–1625. doi:10.1002/bjs.10247

van Mastrigt, G. A. P. G., Hiligsmann, M., Arts, J. J. C., Broos, P. H., Kleijnen, J., Evers, S. M. A. A., et al. (2016). How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: A five-step approach (part 1/3). *Expert Rev. pharmacoecon. Outcomes Res.* 16, 689–704. doi:10.1080/14737167.2016.1246960

Wagmiller, J. A., Griggs, J. J., Dick, A. W., and Sahasrabudhe, D. M. (2006). Individualized strategy for dosing luteinizing hormone-releasing hormone agonists for androgen-independent prostate cancer: Identification of outcomes and costs. *J. Oncol. Pract.* 2, 57–66. doi:10.1200/JOP.2006.2.2.57

Wailoo, A. J., Bansback, N., Brennan, A., Michaud, K., Nixon, R. M., and Wolfe, F. (2008). Biologic drugs for rheumatoid arthritis in the medicare program: A cost-effectiveness analysis. *Arthritis Rheum.* 58, 939–946. doi:10.1002/art.23374

Waliszewski, M., Rosenberg, M., Rittger, H., Breul, V., and Krackhardt, F. (2020). Endpoint selection for noninferiority percutaneous coronary intervention trials: A methodological description. *Ther. Adv. Cardiovasc. Dis.* 14, 1753944720911329. doi:10.1177/1753944720911329

Welte, R., Feenstra, T., Jager, H., and Leidl, R. (2004). A decision chart for assessing and improving the transferability of economic evaluation results between countries. *PharmacoEconomics* 22, 857–876. doi:10.2165/00019053-200422130-00004

Wijnen, B., Van Mastrigt, G., Redekop, W. K., Majoie, H., De Kinderen, R., and Evers, S. (2016). How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: Data extraction, risk of bias, and transferability (part 3/3). *Expert Rev. pharmacoecon. Outcomes Res.* 16, 723–732. doi:10.1080/14737167.2016.1246961

Wong, F. K. Y., So, C., Chau, J., Law, A. K. P., Tam, S. K. F., and McGhee, S. (2015). Economic evaluation of the differential benefits of home visits with telephone calls and telephone calls only in transitional discharge support. *Age Ageing* 44, 143–147. doi:10.1093/ageing/afu166

Xie, X., Falk, L., Brophy, J. M., Tu, H. A., Guo, J., Gajic-Veljanoski, O., et al. (2019). A non-inferiority framework for cost-effectiveness analysis. *Int. J. Technol. Assess. Health Care* 35, 291–297. doi:10.1017/S0266462319000576

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 02 March 2023
DOI 10.3389/fphar.2023.1055727

OPEN ACCESS

EDITED BY
Ileana Mardare,
Carol Davila University of Medicine and Pharmacy, Romania

REVIEWED BY
Wenxi Tang,
China Pharmaceutical University, China
Bogdan Vasile Ileanu,
Independent researcher, Bucharest, Romania

*CORRESPONDENCE
Shunping Li,
lishunping@sdu.edu.cn

SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 28 September 2022
ACCEPTED 20 February 2023
PUBLISHED 02 March 2023

CITATION
Liu S, Dou L and Li S (2023), Cost-effectiveness analysis of PD-1 inhibitors combined with chemotherapy as first-line therapy for advanced esophageal squamous-cell carcinoma in China. *Front. Pharmacol.* 14:1055727. doi: 10.3389/fphar.2023.1055727

Cost-effectiveness analysis of PD-1 inhibitors combined with chemotherapy as first-line therapy for advanced esophageal squamous-cell carcinoma in China

Shixian Liu[1,2,3], Lei Dou[1,2,3] and Shunping Li[1,2,3]*

[1]Centre for Health Management and Policy Research, School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan, China, [2]NHC Key Laboratory of Health Economics and Policy Research (Shandong University), Jinan, China, [3]Center for Health Preference Research, Shandong University, Jinan, China

Objective: This study was aimed to investigate the cost-effectiveness of all available programmed death 1 (PD-1) inhibitors combined with chemotherapy in the first-line treatment of advanced esophageal squamous-cell carcinoma (ESCC) from the Chinese healthcare system perspective.

Methods: A partitioned survival model with a 3-week cycle and a 10-year time horizon was constructed based on a network meta-analysis. The survival data and utility values were derived from clinical trials, and the direct medical costs were collected from public drug bidding database and published literature. Total costs, quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) were calculated. Scenario, one-way and probabilistic sensitivity analyses were performed to assess the uncertainty around model parameters.

Results: Compared with mono-chemotherapy, toripalimab, sintilimab and camrelizumab plus chemotherapy were cost-effective treatment regimens, while serplulimab, pembrolizumab and nivolumab plus chemotherapy were not cost-effective options. Toripalimab plus chemotherapy provided the highest QALYs of 0.95 with the lower cost of $8,110.53 compared to other competing alternatives. The robustness of the base-case results was confirmed by scenario and one-way sensitivity analysis. At a willingness-to-pay threshold of three times *per capita* gross domestic product ($38,351.20) in 2021, the probability of toripalimab plus chemotherapy being the optimal option was 74.25% compared with other six competing alternatives.

Conclusion: Toripalimab plus chemotherapy represented the most cost-effective option as the first-line therapy for advanced ESCC patients in China.

KEYWORDS

cost-effectiveness, esophageal squamous-cell carcinoma, PD-1 inhibitors, first-line therapy, chemoimmunotherapy

Introduction

Esophageal cancer is the fifth most common malignancy and the fourth leading cause of cancer-related death in China (Sung et al., 2021; Zheng et al., 2022). Esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma represent the predominant histological type, with the former accounting for approximately 85% of cases (Arnold et al., 2020). Many esophageal cancers are unresectable at first diagnosis (Rustgi and El-Serag, 2014). Standard fluoropyrimidine or paclitaxel plus cisplatin-based chemotherapy is recommended as first-line treatment for patients with advanced or metastatic ESCC(Muro et al., 2019). The clinical benefits, however, remain limited in patients with advanced or metastatic ESCC receiving standard of care, with a median overall survival (OS) of fewer than 1 year (Ajani et al., 2019; Shah et al., 2023). Therefore, discovering revolutionary treatment strategies to improve prognosis becomes a pressing need in these populations.

In recent years, immune checkpoint inhibitors targeting programmed death 1 (PD-1) or programmed death-ligand 1 (PD-L1) have emerged as promising antitumor regimens across multiple malignancies, including esophageal cancer (Constantinidou et al., 2019). Several prior randomized studies have demonstrated that PD-1 blockade provided significant survival benefits as second-line treatment for advanced ESCC(Kato et al., 2019; Huang et al., 2020). Further, ESCORT-first (Luo et al., 2021), CheckMate-648 (Doki et al., 2022), KEYNOTE-590 (Sun et al., 2021), ORIENT-15 (Lu et al., 2022) and JUPITER-06 (Wang et al., 2022) respectively confirmed that camrelizumab, nivolumab, pembrolizumab, sintilimab and toripalimab combined with chemotherapy produced encouraging antitumor activity compared with mono-chemotherapy. As a result, the five chemoimmunotherapies mentioned above have been in succession approved by the National Medical Products Administration and recommended by the Guidelines of Chinese Society of Clinical Oncology (CSCO, 2022). In 2021, Camrelizumab officially entered the National Reimbursement Drug List (NRDL) negotiation through an 85.2% price reduction for patients with locally advanced or metastatic ESCC, which has progressed after first-line chemotherapy (Cai et al., 2021). The other PD-1 inhibitors covered by the NRDL, such as sintilimab and toripalimab, did not yet include indications related to esophageal cancer.

A published network meta-analysis (NMA) involving five clinical trials with 3,163 patients has investigated the efficacy and safety differences between diverse chemoimmunotherapies in first-line treatment for advanced ESCC (Li et al., 2022). The results proved that toripalimab plus chemotherapy achieved the longest OS [hazard ratio (HR): 0.58, 95% confidence interval (CI): 0.43–0.78], while camrelizumab and sintilimab combined with chemotherapy engendered the longest progression-free survival (PFS) (HR: 0.56, 95% CI: 0.46–0.68) than other treatment examined (Li et al., 2022). Recently, the ASTRUM-007 trial revealed that serplulimab plus chemotherapy significantly improved PFS (HR: 0.60, 95% CI: 0.48–0.75) and OS (HR: 0.68, 95% CI: 0.53–0.87) *versus* mono-chemotherapy for advanced ESCC, but with a manageable safety profile (Song et al., 2023). Considering the lack of head-to-head clinical trials, clinicians confronted insurmountable quandaries in making appropriate treatment options for a given patient based on the available evidence alone, and that is before taking into account relative costs. Therefore, with the enthusiasm of health technology agencies towards life-cycle health technology assessment (Drummond et al., 2008), the selection of optimal treatment options for decision-makers essentially depended on comparative cost-effectiveness (Sanders et al., 2016; Dai et al., 2022).

Most published economic evaluations have assessed the cost-effectiveness of camrelizumab (Zhang et al., 2021), nivolumab (Liu et al., 2022), pembrolizumab (Zhu et al., 2022a) and sintilimab (Ye et al., 2022) compared to chemotherapy in the first-line setting for advanced ESCC. However, the cost-effectiveness between all available first-line chemoimmunotherapies for patients with advanced ESCC was still uncertain. As such, we aimed to evaluate the cost-effectiveness of all first-line chemoimmunotherapies for the treatment of advanced or metastatic ESCC, namely, camrelizumab, nivolumab, pembrolizumab, serplulimab, sintilimab, and toripalimab combined with chemotherapy, and mono-chemotherapy, from the perspective of Chinese healthcare system to better inform reimbursement policy and achieve optimal health resource allocation.

Methods

Patients and treatment

This study was guided by the Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) updated reporting guidelines (Supplementary Table S1) (Husereau et al., 2022). This economic evaluation was based on modelling techniques and published literature, and did not require approval of the institutional research ethics board because no real human participants or animals were involved.

A hypothetical cohort of patients, aged at least 18 years, with histologically or cytologically confirmed unresectable locally advanced, recurrent, or metastatic ESCC with the same characteristics as those patients enrolled in ESCORT-first (Luo et al., 2021), CheckMate-648 (Doki et al., 2022), KEYNOTE-590 (Sun et al., 2021), ASTRUM-007 (Song et al., 2023), ORIENT-15 (Lu et al., 2022) and JUPITER-06 (Wang et al., 2022) clinical trials. Eligible patients received one of seven first-line interventions: (1) Chemotherapy (Cisplatin, 75 mg/m^2, day 1 plus Paclitaxel, 175 mg/m^2, day 1 or Fluorouracil, 800 mg/m^2, days 1 through 5; 3-week); (2) Camrelizumab (200 mg; 3-week) plus chemotherapy; (3) Nivolumab (240 mg; 2-week) plus chemotherapy; (4) Pembrolizumab (200 mg; 3-week) plus chemotherapy; (5) Serplulimab (75 mg/kg; 2-week) plus chemotherapy; (6) Sintilimab (200 mg; 3-week) plus chemotherapy; (7) Toripalimab (240 mg; 3-week) plus chemotherapy (Supplementary). After disease progression, we assumed that the remaining patients would receive subsequent best supportive anti-cancer regimens to accurately capture the cost-effectiveness associated with first-line treatment.

Model construction

A partitioned survival model was constructed with three exclusive health states [PFS, progression-disease (PD), and death]

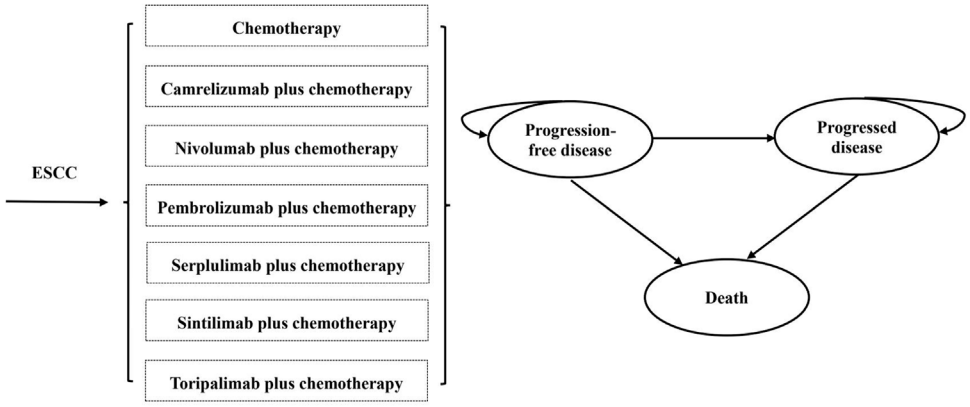

FIGURE 1
The structure of the partitioned survival model. (ESCC, esophageal squamous-cell carcinoma).

to portray disease progression and treatment efficacy (Figure 1). The cycle length was 3 weeks, which was consistent with the treatment protocol in clinical trials, and half-cycle correction was implemented to calibrate the timing of events. The 10-year time horizon was adequate to guarantee that ESCC patients completely entered the terminal state. The primary endpoint of the model included overall costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs; incremental cost per additional QALY gained) for pairwise comparison between chemoimmunotherapy-related groups. According to China Guidelines for Pharmacoeconomic Evaluations, a discount of 5% was applied to health outcomes and costs beyond the first year over the time horizon (Liu et al., 2020). All costs were adjusted to 2022 prices with the local Consumer Price Index and converted into US dollars (1$ = 6.33 CNY). As recommended by the World Health Organization (Marseille et al., 2015), 3 times *per capita* gross domestic product (GDP) in China in 2021 ($38,351.20) was implemented as the willingness-to-pay (WTP) threshold to investigate the most cost-effective competing alternatives.

Clinical inputs

As a result of the absence of head-to-head clinical trials comparing chemotherapy and all available chemoimmunotherapies, a systematic review was conducted in February 2023 to identify randomized controlled trials (RCTs) of relevant treatment strategies in advanced ESCC. Web of Science, PubMed, Embase, and Cochrane Library databases were searched using search terms: "camrelizumab or nivolumab or pembrolizumab or serplulimab or sintilimab or toripalimab or PD-1 or PD-L1", "chemotherapy", "esophageal squamous cell cancer or esophageal cancer or esophageal carcinoma" and "randomized clinical trial or randomized controlled trial". The literature search identified 157 publications (Supplementary Figure S1). After rigorous screening, a total of six relevant phase III RCTs with 3,683 patients were included in the systematic review and network meta-analysis. The basic characteristics and bias risk assessment of included studies were summarized in Supplementary Table S2, Figure S2. The results of the network meta-analysis were shown in Supplementary Table S3.

GetData Graph Digitizer 2.26 (http://www.getdata-graph-digitizer.com/) was applied to extract PFS and OS data points from the Kaplan-Meier curves reported in the six RCTs (Supplementary Table S4, S5). To optimally extrapolate the lifetime survival outcome, Guyot's parametric survival models were considered for each endpoint of chemotherapy (Guyot et al., 2012), including Exponential, Weibull, Log-logistic, Log-normal, and Gompertz distributions (Supplementary Table S6, Figures S3, S4). Weibull distribution provided eligible survival function based on clinical plausibility, statistical goodness-of-fit (Akaike Information Criterion and Bayesian Information Criterion), and visual examination (Latimer, 2013). The estimated shape parameters (γ) and scale parameters (λ) were shown in Table 1.

The baseline hazards for chemotherapy were estimated by averaging the patient survival data fitted by Weibull distribution (Supplementary Figure S5). We then derived the expected survival curves for chemoimmunotherapies by applying the HRs to the reference arm of chemotherapy. The Weibull parameter γ for chemoimmunotherapies was equal to the reference arm, and the Weibull parameter λ for chemoimmunotherapies was calculated as λ for reference arm multiplied by the HRs between alternative treatments and mono-chemotherapy (Hoyle et al., 2010).

Cost inputs

Our model considered only direct medical costs, which included drug costs, subsequent treatment, hospitalization expense, routine follow-up and radiological examinations, and administration costs associated with adverse events (AEs) (Table 2). To estimate drug costs, we calculated the average winning bids in 2023 from YAOZHI database (https://data.yaozh.com/), which aggregated the latest price data around the country. The default height of 165 cm and body weight of 65 kg, with an average body surface area (BSA) of 1.72 m^2 were assumed for the Chinese ESCC patients to determine the dosage and expenditure of chemotherapies (Liu et al., 2022). Other healthcare-related costs were retrieved from recently

TABLE 1 Key clinical inputs.

Parameters	Baseline value	Range		Distribution	References
		Minimum	Maximum		
Weibull parameters of PFS and OS for chemotherapy					
ASTRUM 007-PFS	shape: 0.02976800	NA	NA	Weibull	Song et al. (2023)
	scale: 0.45033640				
ASTRUM 007-OS	shape: 0.00768000	NA	NA	Weibull	Song et al. (2023)
	scale: 0.42383320				
CheckMate 648-PFS	shape: 0.0560388	NA	NA	Weibull	Doki et al. (2022)
	scale: 0.1856546				
CheckMate 648-OS	shape: 0.0176300	NA	NA	Weibull	Doki et al. (2022)
	scale: 0.2662113				
ESCORT 1st-PFS	shape: 0.01904830	NA	NA	Weibull	Luo et al. (2021)
	scale: 0.53355410				
ESCORT 1st-OS	shape: 0.00453990	NA	NA	Weibull	Luo et al. (2021)
	scale: 0.54763450				
JUPITER 06-PFS	shape: 0.02086470	NA	NA	Weibull	Wang et al. (2022)
	scale: 0.56311860				
JUPITER 06-OS	shape: 0.00377300	NA	NA	Weibull	Wang et al. (2022)
	scale: 0.60823730				
ORIENT 15-PFS	shape: 0.02568620	NA	NA	Weibull	Lu et al. (2022)
	scale: 0.41099730				
ORIENT 15-OS	shape: 0.00839040	NA	NA	Weibull	Lu et al. (2022)
	scale: 0.42212310				
HR of PFS in comparison with chemotherapy					
Camrelizumab plus chemotherapy	0.56	0.46	0.68	Log-normal	NMA
Nivolumab plus chemotherapy	0.81	0.64	1.04	Log-normal	NMA
Pembrolizumab plus chemotherapy	0.65	0.54	0.78	Log-normal	NMA
Serplulimab plus chemotherapy	0.60	0.48	0.75	Log-normal	NMA
Sintilimab plus chemotherapy	0.56	0.46	0.68	Log-normal	NMA
Toripalimab plus chemotherapy	0.58	0.46	0.74	Log-normal	NMA
HR of OS in comparison with chemotherapy					
Camrelizumab plus chemotherapy	0.70	0.56	0.88	Log-normal	NMA
Nivolumab plus chemotherapy	0.74	0.58	0.96	Log-normal	NMA
Pembrolizumab plus chemotherapy	0.72	0.60	0.88	Log-normal	NMA
Serplulimab plus chemotherapy	0.68	0.53	0.87	Log-normal	NMA
Sintilimab plus chemotherapy	0.63	0.51	0.78	Log-normal	NMA
Toripalimab plus chemotherapy	0.58	0.43	0.78	Log-normal	NMA
Risk of severe adverse events (%)					
Chemotherapy[#]					

(Continued on following page)

TABLE 1 (*Continued*) Key clinical inputs.

Parameters	Baseline value	Range		Distribution	References
		Minimum	Maximum		
Anemia	10.61	8.49	12.73	Beta	Average value
Neutropenia	25.36	20.29	30.43	Beta	Average value
Leukopenia	12.58	10.07	15.10	Beta	Average value
Nausea	6.49	5.19	7.78	Beta	Average value
Hypokalemia	6.61	5.29	7.94	Beta	Average value
Camrelizumab plus chemotherapy					
Anemia	17.45	13.96	20.94	Beta	Luo et al. (2021)
Leukopenia	24.16	19.33	28.99	Beta	Luo et al. (2021)
Neutropenia	39.93	31.95	47.92	Beta	Luo et al. (2021)
Nivolumab plus chemotherapy					
Stomatitis	6.45	5.16	7.74	Beta	Doki et al. (2022)
Anemia	9.68	7.74	11.61	Beta	Doki et al. (2022)
Neutropenia	8.06	6.45	9.68	Beta	Doki et al. (2022)
Pembrolizumab plus chemotherapy					
Nausea	7.03	5.62	8.43	Beta	Sun et al. (2021)
Anemia	12.43	9.95	14.92	Beta	Sun et al. (2021)
Fatigue	6.22	4.97	7.46	Beta	Sun et al. (2021)
Neutropenia	22.70	18.16	27.24	Beta	Sun et al. (2021)
Vomiting	6.22	4.97	7.46	Beta	Sun et al. (2021)
Stomatitis	5.68	4.54	6.81	Beta	Sun et al. (2021)
Leukopenia	8.65	6.92	10.38	Beta	Sun et al. (2021)
Hyponatraemia	5.41	4.32	6.49	Beta	Sun et al. (2021)
Serplulimab plus chemotherapy					
Anemia	17.54	14.03	21.05	Beta	Song et al. (2023)
Leukopenia	11.26	9.01	13.51	Beta	Song et al. (2023)
Neutropenia	18.59	14.87	22.30	Beta	Song et al. (2023)
Sintilimab plus chemotherapy					
Anemia	12.54	10.03	15.05	Beta	Lu et al. (2022)
Leukopenia	17.43	13.94	20.92	Beta	Lu et al. (2022)
Neutropenia	29.97	23.98	35.96	Beta	Lu et al. (2022)
Toripalimab plus chemotherapy					
Anemia	10.89	8.72	13.07	Beta	Wang et al. (2022)
Leukopenia	20.23	16.19	24.28	Beta	Wang et al. (2022)
Neutropenia	42.41	33.93	50.89	Beta	Wang et al. (2022)
Pneumonia	5.84	4.67	7.00	Beta	Wang et al. (2022)

#, The incidence of adverse events associated with the chemotherapy group was derived from the mean of ESCORT-first, CheckMate-648, KEYNOTE-590, ASTRUM-007, ORIENT-15, and JUPITER-06, clinical trials; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; NMA, network meta-analysis.

TABLE 2 Basic parameters input to the model and the ranges of the sensitivity analyses.

Parameters	Baseline value	Range		Distribution	References
		Minimum	Maximum		
Cost inputs (US $)					
Camrelizumab (200 mg)	462.25	369.80	554.69	Gamma	YaoZH (2023)
Nivolumab (100 mg)	1460.30	1168.24	1752.36	Gamma	YaoZH (2023)
Pembrolizumab (100 mg)	2828.73	2262.98	3394.47	Gamma	YaoZH (2023)
Serplulimab (100 mg)	882.18	705.74	1058.62	Gamma	YaoZH (2023)
Sintilimab (100 mg)	170.50	136.40	204.60	Gamma	YaoZH (2023)
Toripalimab (240 mg)	302.00	241.60	362.40	Gamma	YaoZH (2023)
Cisplatin (10 mg)	1.47	1.18	1.77	Gamma	YaoZH (2023)
Paclitaxel (30 mg)	10.61	8.49	12.73	Gamma	YaoZH (2023)
Fluorouracil (250 mg)	8.51	6.81	10.22	Gamma	YaoZH (2023)
Cost of best supportive care	182.23	145.78	218.68	Gamma	Liu et al. (2022)
Hospitalization expense	19.86	15.89	12.83	Gamma	Shen et al. (2022)
Routine follow-up cost	73.72	58.98	88.47	Gamma	Liu et al. (2022)
Cost of laboratory tests and radiological examinations	357.34	285.87	428.81	Gamma	Liu et al. (2022)
Management cost of Anemia	336.63	269.30	403.95	Gamma	Zhan et al. (2022)
Management cost of Neutropenia	454.26	363.41	545.11	Gamma	Liu et al. (2022)
Management cost of Leukopenia	454.26	363.41	545.11	Gamma	Liu et al. (2022)
Management cost of Stomatitis	46.54	37.23	55.85	Gamma	Liu et al. (2022)
Management cost of Nausea	101.15	80.92	121.38	Gamma	Zhan et al. (2022)
Management cost of Fatigue	113.59	90.87	136.31	Gamma	Liu et al. (2022)
Management cost of Vomiting	101.15	80.92	121.38	Gamma	Zhan et al. (2022)
Management cost of Hyponatraemia	3223.00	2578.40	3867.60	Gamma	Shao et al. (2022)
Management cost of Pneumonia	1640.00	1312.00	1968.00	Gamma	Shao et al. (2022)
Management cost of Hypokalemia	3000.00	2400.00	3600.00	Gamma	Assumption
Utility inputs					
Utility of PFS	0.75	0.60	0.90	Beta	Wilke et al. (2014)
Utility of progression-disease	0.60	0.48	0.72	Beta	Wilke et al. (2014)
Disutility of Anemia	0.07	0.06	0.09	Beta	Cai et al. (2021)
Disutility of Neutropenia	0.20	0.16	0.24	Beta	Nafees et al. (2017)
Disutility of Leukopenia	0.20	0.16	0.24	Beta	Nafees et al. (2017)
Disutility of Stomatitis	0.15	0.12	0.18	Beta	Lloyd et al. (2006)
Disutility of Nausea	0.13	0.10	0.15	Beta	Nafees et al. (2017)
Disutility of Fatigue	0.07	0.05	0.08	Beta	Nafees et al. (2017)
Disutility of Vomiting	0.13	0.10	0.15	Beta	Nafees et al. (2017)
Disutility of Hyponatraemia	0.03	0.02	0.04	Beta	Shao et al. (2022)
Disutility of Pneumonia	0.05	0.04	0.06	Beta	Shao et al. (2022)
Disutility of Hypokalemia	0.03	0.02	0.04	Beta	Assumption

(Continued on following page)

TABLE 2 (*Continued*) Basic parameters input to the model and the ranges of the sensitivity analyses.

Parameters	Baseline value	Range		Distribution	References
		Minimum	Maximum		
Others					
Discount rate (%)	5.00	0.00	8.00	Beta	Liu et al. (2020)
Patient weight (kg)	65.00	52.00	78.00	Gamma	Liu et al. (2022)
Body surface area (m^2)	1.72	1.38	2.06	Gamma	Liu et al. (2022)

published literature (Liu et al., 2022; Shen et al., 2022). Grade 3 or above AEs with an incidence of greater than 5% reported in the clinical trial were included as they exerted a considerable effect on the course of survival and treatment, including anemia, neutropenia, leukopenia, stomatitis, nausea, fatigue, vomiting, hyponatraemia, hypokalemia and pneumonia (Liu et al., 2022; Shao et al., 2022; Zhan et al., 2022). For each treatment regimen, the management cost of serious AEs were determined by multiplying the unite cost (per event) by the corresponding incidence rate.

Health state utility

Health state utilities were estimated based on the EuroQoL five-dimension, three-level questionnaire reported from a double-blind, randomised phase 3 trial, which recruited participants with metastatic or locally advanced gastric or gastro-oesophageal junction adenocarcinoma (Wilke et al., 2014). The baseline utility values for PFS and PD states were 0.75 and 0.60, respectively, which were in compliance with previously published cost-effectiveness analyses (Yang et al., 2021; Liu et al., 2022). The disutility values caused by grade 3 or above treatment-related AEs were considered by multiplying the duration-adjusted disutilities by the prevalence rates of specific AEs (Lloyd et al., 2006; Nafees et al., 2017; Cai et al., 2021; Shao et al., 2022) (Table 2).

Scenario and sensitivity analyses

We performed four scenarios to examine how our model was impacted by time horizon, utility values, BSA and subsequent treatment strategies: first, health utility values from published economic evaluations associated with ESCC were employed to further validate the base-case results (Zhang et al., 2020; Marguet et al., 2021; Zhang et al., 2021); second, shorter time horizon (2, 5, and 8 years) was conducted in this scenario; third, the reasonably lower or higher weight and BSA (58 kg, 1.60 m^2 and 80 kg, 1.98 m^2) were investigated; fourth, according to guidelines and clinical trials (CSCO, 2022), after disease progression, we assumed that the proportion of patients receiving immunotherapy, targeted therapy, chemotherapy and BSC in the chemotherapy and chemoimmunotherapy groups were 10% and 20%, 10% and 10%, 20% and 25%, and 60% and 45%, respectively.

One-way and probabilistic sensitivity analyses (PSA) were conducted for input parameters to explore the robustness of our results. In the one-way sensitivity analyses, the estimated range of variables were either based on reported 95% confidence intervals or determined by assuming a 20% deviation from the base-case values to appraise their degree of impact on ICERs. On the basis of China Guidelines for Pharmacoeconomic Evaluations, the range of discount rate was set as 0%–8% (Liu et al., 2020). The results were represented by Tornado diagrams. For the PSA, 10,000 Monte Carlo simulations was generated by simultaneously sampling all crucial variables from the pre-specified statistical distributions. Gamma distribution was selected for costs, log-normal distribution for HRs between the competing alternatives, and beta distribution for utility values and proportions (Briggs et al., 2012). The results of PSA were presented in cost-effectiveness acceptability curves (CEAC), which illustrated the probabilities of each competing strategy being cost-effective at various WTP thresholds.

Results

Base-case results

The base-case results were shown in Table 3. Compared with mono-chemotherapy, the ICERs of toripalimab, sintilimab, and camrelizumab combined with chemotherapy were $14,047.53/QALY, $18,622.34/QALY, and $29,771.17/QALY, respectively, all were lower than WTP threshold. The ICERs of serplulimab, pembrolizumab, and nivolumab plus chemotherapy *versus* mono-chemotherapy were $170,911.36/QALY, $211,350.41/QALY, and $400,768.95/QALY, respectively, all were more than WTP threshold. In the pairwise comparison between all competing treatments, toripalimab plus chemotherapy yielded the highest QALYs (0.95) with lower cost ($8,110.53) and represented high-value option for advanced ESCC patients at the current price and WTP threshold.

Scenario and sensitivity analyses results

Across all scenario analyses, the general conclusions of the primary analyses were robust and reliable, namely, toripalimab plus chemotherapy was the most cost-effective option against competing regimens (Supplementary Tables S7, S8, S9, S10). One-way sensitivity analyses demonstrated that HR-related parameters, drug costs, utility values and BSA played a considerable role in the base-case results, but alterations in these variables did not significantly alter the conclusion (Supplementary Figure S6). At the WTP thresholds of 3 times *per capita* GDP in China, the CEAC revealed that approximately 74.25%, 23.38%, and 2.37% probabilities of toripalimab, sintilimab, and

TABLE 3 Base-case results.

Strategy	Total cost	QALYs	ICER ($/QALY, pairwise comparison)					
Chemotherapy	4,436.40	0.69	-	-	-	-	-	-
Toripalimab plus chemotherapy	8,110.53	0.95	14,047.53	-	-	-	-	-
Sintilimab plus chemotherapy	8,643.48	0.91	18,622.34	dominated	-	-	-	-
Camrelizumab plus chemotherapy	9,656.62	0.86	29,771.17	dominated	dominated	-	-	-
Serplulimab plus chemotherapy	36,370.68	0.87	170,911.36	dominated	dominated	2,322,505.88	-	-
Pembrolizumab plus chemotherapy	37,312.48	0.84	211,350.41	dominated	dominated	dominated	dominated	-
Nivolumab plus chemotherapy	56,972.21	0.82	400,768.95	dominated	dominated	dominated	dominated	dominated

QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratios.

camrelizumabplus chemotherapy being cost-effective options in simultaneous comparisons of competing strategies (Figure 2).

Discussion

To our knowledge, this is the first study to comprehensively appraise the cost-effectiveness of currently available first-line chemoimmunotherapies for patients with advanced ESCC from the Chinese healthcare system perspective. Our findings indicated that toripalimab, sintilimab, and camrelizumab combined with chemotherapy were cost-effectiveness compared to chemotherapy. Toripalimab plus chemotherapy was the most cost-effective treatment paradigm under the current WTP threshold by virtue of the highest QALYs and lower cost. The base-case results were upheld by the scenario and sensitivity analyses.

Toripalimab was the first approved PD-1 inhibitor developed independently by Chinese pharmaceutical companies, which not only greatly reduced transportation costs compared to imported immunotherapeutic agents, but also provided more substantial price reductions than comparable inhibitors (Tian et al., 2022). Therefore, toripalimab could be more accessible and widely applied for Chinese patients. The NMA demonstrated that sintilimab and camrelizumab plus chemotherapy provided more significant improvements in PFS and OS than nivolumab and pembrolizumab plus chemotherapy. Due to the considerable price advantage and accessibility, sintilimab and camrelizumab plus chemotherapy may be appropriate alternatives for advanced ESCC patients. Serplulimab, a novel domestic PD-1 inhibitor, plus chemotherapy for first-line treatment has not shown an economic advantage, although it may be cost-effective in patients with extensive-stage small cell lung cancer (Zhu et al., 2022b). Therefore, a substantial price reduction for serplulimab was essential to improve patient affordability. Moreover, PD-1 inhibitors plus chemotherapy improved clinical benefits as first-line therapy for advanced ESCC patients, at the cost of greater but controllable toxicity including increased frequency of serious AEs (Li et al., 2022). However, one-way sensitivity analyses showed that these tolerable toxicity-related costs and disutilities exerted a minimal impact on cost-effectiveness and, hence, would not substantially alter the results.

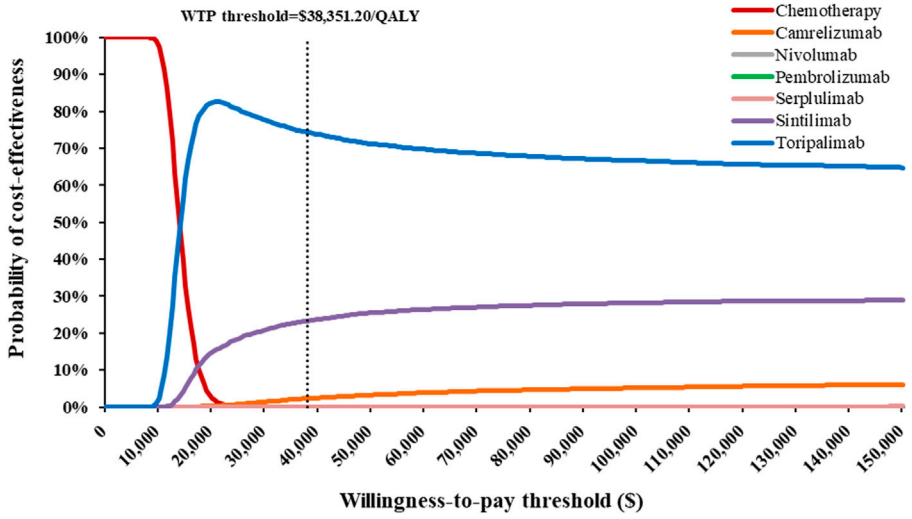

FIGURE 2
Cost-effectiveness acceptability curves indicating the probability of each treatment regimen to be cost-effectiveness in the treatment of advanced esophageal squamous-cell carcinoma at various willingness-to-pay thresholds in China.

In recent years, the Chinese self-developed innovative PD-1 inhibitors have gradually provided better survival benefits, clinical tolerability and cost-effective treatment options for various cancer patients. This situation is mainly driven by the centralized price-negotiated mechanisms to improve the accessibility and afordability of patients (Zhang et al., 2022a; Zhang et al., 2022b). The National Medical Products Administration, previously called the China Food and Drug Administration, has strengthened regulatory capacity and launched a series of priority procedures to expedite the development, review and approval of innovative anti-cancer medicines (Zhou et al., 2017; Zhang et al., 2022a). Furthermore, to temper rapidly increasing costs, value-based pricing and national medical insurance negotiations became critical criterion for innovative drugs to be covered by national medical insurance (Si et al., 2020; Tang et al., 2020). These mechanisms have reduced drug prices by half, safeguarding both patient affordability and the sustainability of medical insurance (Zhang et al., 2022b).

To date, several economic evaluations were relevant to ours and warrant discussion. Zhang et al. (Zhang et al., 2021) estimated the cost-effectiveness of camrelizumab plus chemotherapy in the first-line treatment of advanced or metastatic ESCC based on ESCORT-first clinical trial, and suggested that camrelizumab plus chemotherapy might not be cost-effective compared with standard chemotherapy in China. Nevertheless, this previous assessment used non-negotiated prices for camrelizumab, which are no longer relevant at present, as the medical insurance negotiation mechanism has dramatically improved accessibility for patients. Zhu et al. (Zhu et al., 2022a) and Liu et al. (Liu et al., 2022) evaluated the cost-effectiveness of pembrolizumab and nivolumab combined with chemotherapy from the Chinese healthcare system perspective, respectively, and the conclusions aligned well with those of this analysis. Nivolumab and pembrolizumab combined with chemotherapy was extremely unlikely to be economical compared to chemotherapy (Malmberg et al., 2022), and substantial price reductions or generous patient assistance programs were required to improve affordability (Howard, 2014). The latest economic evidence suggested that sintilimab and toripalimab plus chemotherapy were cost-effective compared with chemotherapy regimens in the first-line treatment of patients with advanced ESCC(Shao et al., 2022; Fang et al., 2023). Our results were consistent with available studies. Camrelizumab, sintilimab, and toripalimab plus chemotherapy were high-value innovative options for advanced ESCC patients in China.

Our study had some limitations that merited discussion, many of which were governed by data availability and model assumptions. Foremost, because the head-to-head clinical trial was unavailable, an indirect comparison was performed based on NMA to evaluate all available chemoimmunotherapies as first-line treatment for advanced ESCC, although there was moderate heterogeneity in the pairwise comparison. Second, we assumed best supportive care as the primary treatment after disease progression, which might be different from the actual clinical situations. Scenario analysis demonstrated that the alternative of subsequent treatment options would not substantially alter the outcome of the base-case analysis. Third, since the utility values of specific health states were limited in China, the utilities and disutilities were determined based on published clinical trial, which might cause some deviations in the cumulative QALYs. Fourth, due to the absence of data, the costs and disutilities associated with grade 1/2 treatment-related AEs were excluded from this model, although one-way sensitivity analyses implied that only minimal impact on the base-case results. Fifth, PD-L1 expression was enriched in ESCC patients. Prior economic evidence indicated that PD-1 inhibitors were potentially more sensitive to PD-L1-positive ESCC patients against overall population (Zhu et al., 2022a; Liu et al., 2022; Shao et al., 2022). Because PD-L1-positive was inconsistently defined across clinical trials, subgroup analyses were not feasible in this study. Consequently, subgroup analyses based on head-to-head trials or real-world data warranted further studies to support healthcare decision-making and precision medicine.

Conclusion

In summary, our findings showed that toripalimab, sintilimab, and camrelizumab combined with chemotherapy were cost-effective treatment options over chemotherapy, and toripalimab plus chemotherapy was the most cost-effective regimen compared with other competing alternatives as the first-line treatment for advanced ESCC patients in China.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

SXL and SPL were responsible for study design, model building and statistical analysis. SXL prepared the manuscript. SXL and LD searched literatures and collected data. All authors critically reviewed the model structure, verified results and revised the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1055727/full#supplementary-material

References

Ajani, J. A., D'Amico, T. A., Bentrem, D. J., Chao, J., Corvera, C., Das, P., et al. (2019). Esophageal and esophagogastric junction cancers, version 2.2019, NCCN clinical practice guidelines in Oncology. *J. Natl. Compr. Canc Netw.* 17 (7), 855–883. doi:10.6004/jnccn.2019.0033

Arnold, M., Ferlay, J., van Berge Henegouwen, M. I., and Soerjomataram, I. (2020). Global burden of oesophageal and gastric cancer by histology and subsite in 2018. *Gut* 69 (9), 1564–1571. doi:10.1136/gutjnl-2020-321600

Briggs, A. H., Weinstein, M. C., Fenwick, E. A., Karnon, J., Sculpher, M. J., Paltiel, A. D., et al. (2012). Model parameter estimation and uncertainty analysis: A report of the ISPOR-SMDM modeling good research practices task force working group-6. *Med. Decis. Mak.* 32 (5), 722–732. doi:10.1177/0272989x12458348

Cai, H., Xu, B., Li, N., Zheng, B., Zheng, Z., and Liu, M. (2021). Cost-effectiveness analysis of camrelizumab versus chemotherapy as second-line treatment of advanced or metastatic esophageal squamous cell carcinoma. *Front. Pharmacol.* 12 (1), 732912. doi:10.3389/fphar.2021.732912

Constantinidou, A., Alifieris, C., and Trafalis, D. T. (2019). Targeting programmed cell death -1 (PD-1) and ligand (PD-L1): A new era in cancer active immunotherapy. *Pharmacol. Ther.* 194 (2), 84–106. doi:10.1016/j.pharmthera.2018.09.008

CSCO (2022). *Guidelines of Chinese society of clinical oncologhy(CSCO) esophageal cancer*. Beijing: People's Medical Publishing House.

Dai, W. F., Beca, J. M., Nagamuthu, C., Liu, N., de Oliveira, C., Earle, C. C., et al. (2022). Cost-effectiveness analysis of pertuzumab with trastuzumab in patients with metastatic breast cancer. *JAMA Oncol.* 8 (4), 597–606. doi:10.1001/jamaoncol.2021.8049

Doki, Y., Ajani, J. A., Kato, K., Xu, J., Wyrwicz, L., Motoyama, S., et al. (2022). Nivolumab combination therapy in advanced esophageal squamous-cell carcinoma. *N. Engl. J. Med.* 386 (5), 449–462. doi:10.1056/NEJMoa2111380

Drummond, M. F., Schwartz, J. S., Jönsson, B., Luce, B. R., Neumann, P. J., Siebert, U., et al. (2008). Key principles for the improved conduct of health technology assessments for resource allocation decisions. *Int. J. Technol. Assess. Health Care* 24 (3), 244–258. doi:10.1017/s0266462308080343

Fang, R., Wang, S., Liu, Y., and Xu, J. (2023). Cost-effectiveness analysis of toripalimab plus paclitaxel and cisplatin as first-line treatment for advanced or metastatic esophageal squamous cell carcinoma. *Adv. Ther*. doi:10.1007/s12325-022-02402-z

Guyot, P., Ades, A. E., Ouwens, M. J., and Welton, N. J. (2012). Enhanced secondary analysis of survival data: Reconstructing the data from published kaplan-meier survival curves. *BMC Med. Res. Methodol.* 12 (1), 9. doi:10.1186/1471-2288-12-9

Howard, D. H. (2014). Drug companies' patient-assistance programs--helping patients or profits? *N. Engl. J. Med.* 371 (2), 97–99. doi:10.1056/NEJMp1401658

Hoyle, M., Green, C., Thompson-Coon, J., Liu, Z., Welch, K., Moxham, T., et al. (2010). Cost-effectiveness of temsirolimus for first line treatment of advanced renal cell carcinoma. *Value Health* 13 (1), 61–68. doi:10.1111/j.1524-4733.2009.00617.x

Huang, J., Xu, J., Chen, Y., Zhuang, W., Zhang, Y., Chen, Z., et al. (2020). Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCORT): A multicentre, randomised, open-label, phase 3 study. *Lancet Oncol.* 21 (6), 832–842. doi:10.1016/s1470-2045(20)30110-8

Husereau, D., Drummond, M., Augustovski, F., de Bekker-Grob, E., Briggs, A. H., Carswell, C., et al. (2022). Consolidated health economic evaluation reporting standards 2022 (CHEERS 2022) statement: Updated reporting guidance for health economic evaluations. *Value Health* 25 (1), 3–9. doi:10.1016/j.jval.2021.11.1351

Kato, K., Cho, B. C., Takahashi, M., Okada, M., Lin, C. Y., Chin, K., et al. (2019). Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): A multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 20 (11), 1506–1517. doi:10.1016/s1470-2045(19)30626-6

Latimer, N. R. (2013). Survival analysis for economic evaluations alongside clinical trials--extrapolation with patient-level data: Inconsistencies, limitations, and a practical guide. *Med. Decis. Mak.* 33 (6), 743–754. doi:10.1177/0272989x12472398

Li, Z. C., Sun, Y. T., Lai, M. Y., Zhou, Y. X., and Qiu, M. Z. (2022). Efficacy and safety of PD-1 inhibitors combined with chemotherapy as first-line therapy for advanced esophageal cancer: A systematic review and network meta-analysis. *Int. Immunopharmacol.* 109 (8), 108790. doi:10.1016/j.intimp.2022.108790

Liu, G., Hu, S., Wu, J., and Wu, J. (2020). *China guidelines for pharmacoeconomic evaluations (2020)*. Beijing: China Market Press.

Liu, S., Dou, L., Wang, K., Shi, Z., Wang, R., Zhu, X., et al. (2022). Cost-effectiveness analysis of nivolumab combination therapy in the first-line treatment for advanced esophageal squamous-cell carcinoma. *Front. Oncol.* 12 (1), 899966. doi:10.3389/fonc.2022.899966

Lloyd, A., Nafees, B., Narewska, J., Dewilde, S., and Watkins, J. (2006). Health state utilities for metastatic breast cancer. *Br. J. Cancer* 95 (6), 683–690. doi:10.1038/sj.bjc.6603326

Lu, Z., Wang, J., Shu, Y., Liu, L., Kong, L., Yang, L., et al. (2022). Sintilimab versus placebo in combination with chemotherapy as first line treatment for locally advanced or metastatic oesophageal squamous cell carcinoma (ORIENT-15): Multicentre, randomised, double blind, phase 3 trial. *BMJ* 377 (17), e068714. doi:10.1136/bmj-2021-068714

Luo, H., Lu, J., Bai, Y., Mao, T., Wang, J., Fan, Q., et al. (2021). Effect of camrelizumab vs placebo added to chemotherapy on survival and progression-free survival in patients with advanced or metastatic esophageal squamous cell carcinoma: The ESCORT-1st randomized clinical trial. *JAMA* 326 (10), 916–925. doi:10.1001/jama.2021.12836

Malmberg, R., Zietse, M., Dumoulin, D. W., Hendrikx, J., Aerts, J., van der Veldt, A. A. M., et al. (2022). Alternative dosing strategies for immune checkpoint inhibitors to improve cost-effectiveness: A special focus on nivolumab and pembrolizumab. *Lancet Oncol.* 23 (12), e552–e561. doi:10.1016/s1470-2045(22)00554-x

Marguet, S., Adenis, A., Delaine-Clisant, S., Penel, N., and Bonastre, J. (2021). Cost-utility analysis of continuation versus discontinuation of first-line chemotherapy in patients with metastatic squamous-cell esophageal cancer: Economic evaluation alongside the E-DIS trial. *Value Health* 24 (5), 676–682. doi:10.1016/j.jval.2020.11.017

Marseille, E., Larson, B., Kazi, D. S., Kahn, J. G., and Rosen, S. (2015). Thresholds for the cost-effectiveness of interventions: Alternative approaches. *Bull. World Health Organ* 93 (2), 118–124. doi:10.2471/blt.14.138206

Muro, K., Lordick, F., Tsushima, T., Pentheroudakis, G., Baba, E., Lu, Z., et al. (2019). Pan-asian adapted ESMO clinical practice guidelines for the management of patients with metastatic oesophageal cancer: A JSMO-ESMO initiative endorsed by CSCO, KSMO, MOS, SSO and TOS. *Ann. Oncol.* 30 (1), 34–43. doi:10.1093/annonc/mdy498

Nafees, B., Lloyd, A. J., Dewilde, S., Rajan, N., and Lorenzo, M. (2017). Health state utilities in non-small cell lung cancer: An international study. *Asia Pac J. Clin. Oncol.* 13 (5), e195–e203. doi:10.1111/ajco.12477

Rustgi, A. K., and El-Serag, H. B. (2014). Esophageal carcinoma. *N. Engl. J. Med.* 371 (26), 2499–2509. doi:10.1056/NEJMra1314530

Sanders, G. D., Neumann, P. J., Basu, A., Brock, D. W., Feeny, D., Krahn, M., et al. (2016). Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second panel on cost-effectiveness in health and medicine. *JAMA* 316 (10), 1093–1103. doi:10.1001/jama.2016.12195

Shah, M. A., Kennedy, E. B., Alarcon-Rozas, A. E., Alcindor, T., Bartley, A. N., Malowany, A. B., et al. (2023). Immunotherapy and targeted therapy for advanced gastroesophageal cancer: ASCO guideline. *J. Clin. Oncol.*, JCO2202331. Jco2202331. doi:10.1200/jco.22.02331

Shao, T., Zhao, M., and Tang, W. (2022). Cost-effectiveness analysis of sintilimab vs. placebo in combination with chemotherapy as first-line therapy for local advanced or metastatic oesophageal squamous cell carcinoma. *Front. Oncol.* 12 (1), 953671. doi:10.3389/fonc.2022.953671

Shen, J., Du, Y., Shao, R., and Jiang, R. (2022). First-line sintilimab plus chemotherapy in locally advanced or metastatic esophageal squamous cell carcinoma: A cost-effectiveness analysis from China. *Front. Pharmacol.* 13 (1), 967182. doi:10.3389/fphar.2022.967182

Si, L., Xu, L., Chen, M., and Jan, S. (2020). Using strategic price negotiations to contain costs and expand access to medicines in China. *BMJ Glob. Health* 5 (1), e002256. doi:10.1136/bmjgh-2019-002256

Song, Y., Zhang, B., Xin, D., Kou, X., Tan, Z., Zhang, S., et al. (2023). First-line serplulimab or placebo plus chemotherapy in PD-L1-positive esophageal squamous cell carcinoma: A randomized, double-blind phase 3 trial. *Nat. Med.* doi:10.1038/s41591-022-02179-2

Sun, J. M., Shen, L., Shah, M. A., Enzinger, P., Adenis, A., Doi, T., et al. (2021). Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): A randomised, placebo-controlled, phase 3 study. *Lancet* 398 (10302), 759–771. doi:10.1016/s0140-6736(21)01234-4

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., et al. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 71 (3), 209–249. doi:10.3322/caac.21660

Tang, M., Song, P., and He, J. (2020). Progress on drug pricing negotiations in China. *Biosci. Trends* 13 (6), 464–468. doi:10.5582/bst.2019.01339

Tian, K., Han, J., Wang, Z., and Chen, J. (2022). Immune checkpoint inhibition in first-line treatment for recurrent or metastatic nasopharyngeal carcinoma: A CAPTAIN-1st and JUPITER-02 trial-based cost-effectiveness analysis. *Oral Oncol.* 128 (5), 105842. doi:10.1016/j.oraloncology.2022.105842

Wang, Z. X., Cui, C., Yao, J., Zhang, Y., Li, M., Feng, J., et al. (2022). Toripalimab plus chemotherapy in treatment-naïve, advanced esophageal squamous cell carcinoma (JUPITER-06): A multi-center phase 3 trial. *Cancer Cell* 40 (3), 277–288.e3. doi:10.1016/j.ccell.2022.02.007

Wilke, H., Muro, K., Van Cutsem, E., Oh, S. C., Bodoky, G., Shimada, Y., et al. (2014). Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW):

A double-blind, randomised phase 3 trial. *Lancet Oncol.* 15 (11), 1224–1235. doi:10.1016/s1470-2045(14)70420-6

Yang, F., Fu, Y., Kumar, A., Chen, M., Si, L., and Rojanasarot, S. (2021). Cost-effectiveness analysis of camrelizumab in the second-line treatment for advanced or metastatic esophageal squamous cell carcinoma in China. *Ann. Transl. Med.* 9 (15), 1226. doi:10.21037/atm-21-1803

YaoZH (2023). The big data service platform for China's health industry: Information Query of Drug Bid Winning. [Online]. Available: https://data.yaozh.com/ (Accessed February 2, 2023).

Ye, Z. M., Xu, Z., Zeng, F. Y., Tang, Z. Q., and Zhou, Q. (2022). Cost-effectiveness analysis of sintilimab combined with chemotherapy versus chemotherapy alone as the first-line treatment for advanced esophageal cancer. *Front. Pharmacol.* 13 (1), 934275. doi:10.3389/fphar.2022.934275

Zhan, M., Xu, T., Zheng, H., and He, Z. (2022). Cost-effectiveness analysis of pembrolizumab in patients with advanced esophageal cancer based on the KEYNOTE-181 study. *Front. Public Health* 10 (1), 790225. doi:10.3389/fpubh.2022.790225

Zhang, P. F., Xie, D., and Li, Q. (2020). Cost-effectiveness analysis of nivolumab in the second-line treatment for advanced esophageal squamous cell carcinoma. *Future Oncol.* 16 (17), 1189–1198. doi:10.2217/fon-2019-0821

Zhang, Q., Wu, P., He, X., Ding, Y., and Shu, Y. (2021). Cost-effectiveness analysis of camrelizumab vs. Placebo added to chemotherapy as first-line therapy for advanced or metastatic esophageal squamous cell carcinoma in China. *Front. Oncol.* 11 (1), 790373. doi:10.3389/fonc.2021.790373

Zhang, Y., Naci, H., Wagner, A. K., Xu, Z., Yang, Y., Zhu, J., et al. (2022a). Overall survival benefits of cancer drugs approved in China from 2005 to 2020. *JAMA Netw. Open* 5 (8), e2225973. doi:10.1001/jamanetworkopen.2022.25973

Zhang, Y., Wei, Y., Li, H., Chen, Y., Guo, Y., Han, S., et al. (2022b). Prices and clinical benefit of national price-negotiated anticancer medicines in China. *Pharmacoeconomics* 40 (7), 715–724. doi:10.1007/s40273-022-01161-7

Zheng, R., Zhang, S., Zeng, H., Wang, S., Sun, K., Chen, R., et al. (2022). Cancer incidence and mortality in China, 2016. *J. Natl. Canc Cent.* 2 (1), 1–9. doi:10.1016/j.jncc.2022.02.002

Zhou, Q., Chen, X. Y., Yang, Z. M., and Wu, Y. L. (2017). The changing landscape of clinical trial and approval processes in China. *Nat. Rev. Clin. Oncol.* 14 (9), 577–583. doi:10.1038/nrclinonc.2017.10

Zhu, Y., Liu, K., Ding, D., Zhou, Y., and Peng, L. (2022a). Pembrolizumab plus chemotherapy as first-line treatment for advanced esophageal cancer: A cost-effectiveness analysis. *Adv. Ther.* 39 (6), 2614–2629. doi:10.1007/s12325-022-02101-9

Zhu, Y., Liu, K., Qin, Q., and Zhu, H. (2022b). Serplulimab plus chemotherapy as first-line treatment for extensive-stage small-cell lung cancer: A cost-effectiveness analysis. *Front. Immunol.* 13 (1), 1044678. doi:10.3389/fimmu.2022.1044678

frontiers | Frontiers in Pharmacology

TYPE Original Research
PUBLISHED 27 April 2023
DOI 10.3389/fphar.2023.1040584

OPEN ACCESS

EDITED BY
Jean-Marie Boeynaems,
Université libre de Bruxelles, Belgium

REVIEWED BY
Alessandro Anselmo,
Policlinico Tor Vergata, Italy
George Bayliss,
Brown University, United States

*CORRESPONDENCE
François R. Girardin,
francois.girardin@chuv.ch
Anna Nicolet,
anna.nicolet@unisante.ch

†These authors share first authorship

SPECIALTY SECTION
This article was submitted to Drugs Outcomes Research and Policies, a section of the journal Frontiers in Pharmacology

RECEIVED 09 September 2022
ACCEPTED 31 March 2023
PUBLISHED 27 April 2023

CITATION
Girardin FR, Nicolet A, Bestard O, Lefaucheur C, Budde K, Halleck F, Brouard S, Giral M, Gourraud P-A, Horcholle B, Villard J, Marti J and Loupy A (2023), Immunosuppressant drugs and quality-of-life outcomes in kidney transplant recipients: An international cohort study (EU-TRAIN). *Front. Pharmacol.* 14:1040584. doi: 10.3389/fphar.2023.1040584

Immunosuppressant drugs and quality-of-life outcomes in kidney transplant recipients: An international cohort study (EU-TRAIN)

François R. Girardin[1,2*†], Anna Nicolet[3*†], Oriol Bestard[4], Carmen Lefaucheur[5,6], Klemens Budde[7], Fabian Halleck[8], Sophie Brouard[9], Magali Giral[9], Pierre-Antoine Gourraud[9], Béatrice Horcholle[5], Jean Villard[10], Joachim Marti[3] and Alexandre Loupy[6,11] on behalf of the EU-TRAIN Consortium

[1]Division of Clinical Pharmacology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital, Faculty of Medicine, University of Lausanne, Lausanne, Switzerland, [2]Division of Clinical Pharmacology and Toxicology, Department of Anesthesiology, Clinical Pharmacology, Intensive Care and Emergency Medicine, Geneva University Hospitals, Geneva, Switzerland, [3]Center for Primary Care and Public Health (UniSanté), University of Lausanne, Lausanne, Switzerland, [4]Department of Nephrology and Kidney Transplantation, Vall d'Hebron Hospital Universitari, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, Barcelona, Spain, [5]Kidney Transplant Department, Saint Louis Hospital, Unité de Recherche Clinique, Assistance Publique-Hôpitaux de Paris, Paris, France, [6]Paris Translational Research Center for Organ Transplantation, Institut National de la Santé et de la Recherche Médicale UMR-S970, Université de Paris, Paris, France, [7]Department of Nephrology and Intensive Care, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany, [8]Department of Nephrology and Intensive Care, Charité Virchow Clinic, University Hospital, Berlin, Germany, [9]Nantes Université, INSERM, CRT2I—Center for Research in Transplantation and Translational Immunology, Nantes, France, [10]Transplantation Immunology Unit, National Reference Laboratory for Histocompatibility, Geneva University Hospitals and University of Geneva, Geneva, Switzerland, [11]Kidney Transplant Department, Necker Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France

Introduction: Patient-Reported Outcomes (PRO) integrate a wide range of holistic dimensions that arenot captured within clinical outcomes. Particularly, from induction treatment to maintenance therapy, patient quality-of-life (QoL) of kidney transplant recipients have been sparsely investigated in international settings.

Methods: In a prospective, multi-centric cohort study, including nine transplant centers in four countries, we explored the QoL during the year following transplantation using validated elicitation instruments (EQ-5D-3L index with VAS) in a population of kidney transplant patients receiving immunosuppressive therapies. Calcineurin inhibitors (tacrolimus and ciclosporin), IMPD inhibitor (mycophenolate mofetil), and mTOR inhibitors (everolimus and sirolimus) were the standard-of-care (SOC) medications, together with tapering glucocorticoid therapy. We used EQ-5D and VAS data as QoL measures alongside descriptive statistics at inclusion, per country and hospital center. We computed the proportions of patients with different immunosuppressive therapy patterns, and using bivariate and multivariate analyses, assessed the variations of EQ-5D and VAS between baseline (i.e., inclusion Month 0) and follow up visits (Month 12).

Results: Among 542 kidney transplant patients included and followed from November 2018 to June 2021, 491 filled at least one QoL questionnaire at least at baseline (Month 0). The majority of patients in all countries received tacrolimus and mycophenolate mofetil, ranging from 90.0% in Switzerland and Spain to 95.8% in Germany. At M12, a significant proportion of patients switched immunosuppressive drugs, with proportion varying from 20% in Germany to 40% in Spain and Switzerland. At visit M12, patients who kept SOC therapy had higher EQ-5D (by 8 percentage points, $p < 0.05$) and VAS (by 4 percentage points, $p < 0.1$) scores than switchers. VAS scores were generally lower than EQ-5D (mean 0.68 [0.5–0.8] vs. 0.85 [0.8–1]).

Discussion: Although overall a positive trend in QoL was observed, the formal analyses did not show any significant improvements in EQ-5D scores or VAS. Only when the effect of a therapy use was separated from the effect of switching, the VAS score was significantly worse for switchers during the follow up period, irrespective of the therapy type. If adjusted for patient characteristics and medical history (e.g., gender, BMI, eGRF, history of diabetes), VAS and EQ-5D delivered sound PRO measures for QoL assessments during the year following renal transplantation.

KEYWORDS

immunosuppressant, kidney transplant patient, quality of life, PROMS, VAS (analog visual scale), EQ5D 3L, transplantation, international cohort study

1 Introduction

Kidney transplantation remains the treatment of choice for chronic renal failure. Monitoring procedures and indicators after organ transplantation generally include surgical suite, long-term survival, and complication rates. Monitoring quality-of-life (QoL) is gaining importance as complementary outcome measures, especially because of the need of real-world data on patient wellbeing and intense resource utilization. Clinicians, researchers, and health authorities acknowledge the importance of considering patient-reported outcomes (PROs) alongside biomarkers or genetic characteristics, as multidimensional aspects of individualized treatments and for further health technology assessment (HTA) purposes. Research into health services recently focused on improving patients' health-related QoL, particularly if long-term and expensive therapies with narrow therapeutic index are used: standardized and validated elicitation instruments are needed to derive patient-reported outcome measures (PROMs). PROMs integrate a wide range of multidimensional effects related to the initiation of immunosuppressive drugs and maintenance protocols, including health utility indexes. However, they have been sparsely considered before and after transplantation in international cohort studies, including kidney transplant recipients (KTR). Principal goals of the EU-TRAIN consortium regarding PROMs are: to provide multidimensional findings for translation to end users (clinicians and KTR), to address unmet needs on new biomarker-guided therapies, and to fill the gap related to the preponderant role of immune-suppressants on QoL.

There are disease-specific questionnaires developed for transplant patients or individuals with chronic renal failure, such as the Modified Transplant Symptom Occurrence and Symptom Distress scale derived from 59 items (MTSOSD-59R) (Kim and Jang, 2020) or the Kidney Disease and Quality-of-Life (KDQOL-36) (Chong et al., 2018). The implementation of such elicitation instruments in a routine QoL survey during follow-up (FU) visits remained difficult to achieve in larger scale, due to the number of items, language issues, and nuances between proposals in the questionnaires.

This first study aims to describe QoL in a multi-centric population of patients receiving immunosuppressive therapies to sustain kidney transplantation and contain organ rejection, by implementing PROMs based on validated short questionnaires, such as the EQ-5D-3L index and the Visual Analogue Scale (VAS) score.

2 Materials and methods

2.1 Participants

The EU-TRAIN (EUropean TRAnsplantation and Innovation) prospective cohort of kidney transplant patients is a Consortium for Research and Innovation Framework Programme H2020 that includes four countries (France, Germany, Spain, and Switzerland) and nine transplantation centers based in university hospitals.

Briefly, EU-TRAIN (https://eu-train-project.eu/) was an international, multicenter, prospective trial aiming at implementing the use of clinical decision support system to 1) evaluate non-invasive biomarkers in peripheral blood predicting anti-donor immunological activation, to 2) monitor the risk of transplant rejection without invasive procedures and measure improvement in therapy response after kidney transplantation. Eventually, we aim to assess the effectiveness and QoL and, ultimately, cost-effectiveness of the new diagnostic and monitoring approaches to improve productive and allocative efficiency in European healthcare systems.

More specifically, the primary objectives were 1) the stratification of KTR using non-invasive biomarkers for the risk of allograft rejection in the first year post transplant; 2) the re-classification of rejection diagnoses (SOC histopathology procedures) by the gene expression profiling in allograft biopsies ("Low-risk" and "High-risk" clusterings).

From November 2018 to June 2021, the total patient population included 542 KTR, out of which 491 KTR categorized by age, gender, current medications, physical characteristics (e.g., weight, height), medical history, estimated Glomerular Filtration Rate (eGFR) that determines the stage of kidney disease and the type of allograft donor. A wide range of non-invasive biomarkers will be prospectively assessed, such as T- and B-cell ELISpot assays, donor specific antibodies, blood targeted transcriptional profiling, donor-derived cell-free DNA (liquid biopsy), and ultimately AI-based predictors (e.g., algorithms, machine learning). Main indications to KT were glomerulopathy 19% (n = 104), polycystic kidney disease 14% (n = 75), chronic interstitial nephropathy 13% (n = 69), vascular nephropathy 12% (n = 63), and mixed origins 10% (n = 55). Further etiologies were post-renal diseases 5% (n = 26), diabetes 4% (n = 23), IgA nephropathy 4% (n = 23), and malformative nephropathy 4% (n = 20). All other causes represented 15% (n = 84).

The number of living donors were 107 (20%), 457 KTR (84%) had dialysis before kidney transplantation, and the average duration of dialysis was 3.3 years (min. 0.1 - max. 35 years).

During the 3 months following KT (M3), the rate of biopsies was 60% (n = 327) and biopsy proven acute rejection (BPAR) was 7% (n = 24). Between M3 and 12 months (M12), the rate of performed biopsy was 61% (n = 330) and BPAR was 6% (n = 21). CMV (Cytomegalovirus) reactivation was found in 11% of KTR (n = 60). The rate of BK virus (BKV) reactivation was 5% (n = 28) and BKV-associated nephropathy was found in 4% of KTR (n = 22). At M12, the total number of reported infections (outside BKV and CMV) was 821, the gastrointestinal events 361, and the total number of adverse drug events (ADE) was 3,553 (antibiotics and antifungal medications were the main agents responsible for ADE, n = 755).

Some indicators were not available from the KTR cohort due to the missing observations related to the COVID-19 pandemic and the relatively short observational period.

Local institutional ethics committee approvals were obtained for all nine centers.

2.2 Instruments

We used EQ-5D-3L instrument with permission from the EuroQol Group and VAS scale to measure patients' QoL (Rabin and de Charro, 2001; Rabin et al., 2014). The EQ-5D-3L provides a simple description of patient self-perceived health status covering five health dimensions: Mobility, self-care, usual activities, pain/discomfort and anxiety/depression, with three response options (no problems, some problems, and severe problems). The patient response is transformed into a code with underlying value ranging from perfect health to worst possible health, and the EuroQol Group has already developed a methodology for eliciting value sets for the 3L version in most European countries. We used the value sets for France (Chevalier and de Pouvourville, 2013), Spain (Badia et al., 2001) and Germany (Greiner et al., 2005) in this study to derive EQ-5D scores. Whilst there is no EQ-5D-3L value set available for French-speaking part of Switzerland (Geneva), we used the value set from France as we considered it the most comparable to the patient and hospital settings in Geneva.

The self-reported VAS measures the patient health state and general wellbeing on a scale from 0 to 100, where 0 reflects the worst imaginable health status and 100 the best health status. It is a health summary score used in the clinical and economic evaluation of healthcare as well as in population health surveys (Dolan, 1997; Kullberg et al., 2005).

2.3 Study medication

In this prospective observational study, no therapeutic intervention was assessed. KTR received immunosuppressants after transplantation according to immunosuppressive protocols based on international standards. The following immunosuppressants were used as maintenance therapy to control graft rejection: Calcineurin inhibitors (tacrolimus (Tac) or ciclosporin (Cic), mutually exclusive prescription); IMPD inhibitors (mycophenolate mofetil (Mmf); and mTOR inhibitors (everolimus, sirolimus, mutually exclusive prescription).

Generally, KTR received first Tac, while fewer ones got Cic, together with Mmf as SOC. In cases of signs of nephrotoxicity, allograft rejection or certain infections, such as CMV) or BKV, or progression of neoplasms (Iaria et al., 2007), immunosuppressant therapies were switched or mTor inhibitor was added as a second line treatment.

2.4 Procedure

Elicitation of EQ-5D and VAS estimates were collected at baseline (M0, <24 h before transplantation) and after 1 year (M12). Validated EQ-5D in four languages (English, French, German, Spanish) were used. To ensure harmonization per protocol between countries and transplantation centers, a common eCRF (electronic case report form) was designed and developed by Consortium members. Data was entered by the principal investigators or sub-/co-investigators in the electronic case report form (eCRF), and patient data was anonymized on the electronic case report form (eCRF). Only authorized persons (principal investigators and sub-/co-investigators) were able to access the eCRF at the study sites.

2.5 Data analysis

We derived QoL based on data from EQ-5D and VAS, measured at inclusion (month M = 0) and at FU visit (M12), alongside descriptive statistics at inclusion, per country and hospital center. We calculated the proportions of KTR with different immunosuppressive therapy patterns and non-missing observations at baseline and at FU visit (month M = 12), taking into account those who switched to other therapies over the course of 1 year. We assessed the variation of EQ-5D and VAS scores between baseline (at inclusion) and FU visit (M12).

TABLE 1 Descriptive characteristics of the patient sample at baseline.

	N	Age mean IQR	Gender males	Comor-bidities (yes)	Diabetes history (yes)	Smoking history (yes)	eGFR mean IQR	BMI mean IQR	[a]VAS mean; IQR	[a]EQ-5D mean; IQR
France										
Saint Louis, Paris	130	55.0 [44.0; 67.0]	83 (64%)	129 (99%)	34 (26%)	39 (30%)	12.6 [5.5; 10.9]	24.8 [21.7; 27.1]	0.67 [0.55; 0.8]	0.85 [0.8; 1]
Necker, Paris	138	56.4 [45.0; 68.0]	90 (65%)	136 (99%)	24 (17%)	35 (25%)	9.5 [6.0; 12.0]	25.1 [21.7; 28.1]	0.63 [0.5; 0.8]	0.81 [0.75; 1]
Hôtel Dieu, Nantes	59	58.1 [43.0; 71.0]	34 (58%)	59 (100%)	9 (15%)	32 (54%)	9.3 [7.0; 11.0]	26.1 [22.8; 29.4]	0.68 [0.5; 0.8]	0.84 [0.8; 1]
Bicêtre, Paris	22	58.7 [52.0; 69.0]	12 (55%)	21 (96%)	6 (27%)	5 (23%)	8.1 [7.0; 9.0]	27.7 [25.8; 30.7]	0.71 [0.6; 0.85]	0.81 [0.85; 1]
Germany										
Charité Virchow, Berlin	33	53.2 [44.0; 61.0]	23 (70%)	33 (100%)	4 (12%)	11 (33%)	11.7 [8.05; 14.0]	25.2 [22.5; 26.2]	0.76 [0.7; 0.84]	0.98 [1; 1]
Charité Mitte, Berlin	37	55.9 [48.0; 63.0]	20 (54%)	31 (84%)	1 (3%)	12 (32%)	15.0 [15.0; 15.0]	26.0 [23.0; 28.7]	0.75 [0.7; 0.9]	0.86 [0.89; 1]
Spain										
Bellvitge, Barcelona	48	61.7 [53.0; 69.5]	34 (71%)	48 (100%)	18 (38%)	8 (17%)	17.0 [9.00; 25.0]	28.0 [22.7; 32.3]	0.73 [0.6; 0.8]	0.91 [0.83; 1]
Vall d'Hebron, Barcelona	7	61.7 [49.0; 72.0]	6 (86%)	6 (86%)	3 (43%)	4 (57%)	12.4 [9.0; 20.0]	26.6 [23.8; 27.2]	0.78 [0.7; 0.85]	0.97 [1; 1]
Switzerland										
Geneva hospitals, Geneva	17	55.9 [52.0; 63.0]	12 (71%)	16 (94%)	2 (12%)	7 (41%)	6.6 [5.0; 8.0]	27.1 [22.5; 30.8]	0.70 [0.6; 0.8]	0.90 [0.84; 1]
Total	491	56.7 [47.0; 68.0]	315 (64%)	479 (98%)	101 (21%)	153 (31%)	10.9 [6.2; 13.0]	25.6 [22.1; 28.7]	0.68 [0.5; 0.8]	0.85 [0.8; 1]

eGFR, estimated Glomerular Filtration Rate; BMI, body mass index; VAS, visual analog scale; EQ-5D, measure of health-related quality of life developed by the EuroQol Group with 5 Dimensions; IQR, Interquartile Range (between 25% percentile and 75% percentile).

[a]statistical analysis of means (ANOVA) showed significant differences between countries in their scores of EQ-5D, and VAS at 1% level (F-stat. = 5.73 and F-stat. = 7.67, respectively).

Finally, we investigated associations between QoL measures (EQ-5D and VAS) and types of therapies using generalized linear models, estimated in the FU visit (M12) (GLM, family binomial, link logit, Stata software, 17.0). The unadjusted model results were presented alongside results adjusted for potentially important background explanatory variables: gender, history of diabetes, body mass index (BMI), and estimated renal function at M12. The results of all models were transformed to average marginal effects for ease of interpretation. Average marginal effects show how, on average, a dependent variable (VAS or EQ-5D in our case) changes when the levels of the explanatory variables change (or at a one-unit change of the explanatory variables). Additionally, we explored whether the improvement in QoL over the course of 12 months (measured by EQ-5D or VAS) was associated with immunosuppressive therapies, taking into account cases of switching to other therapies. We used logit models (Stata software, 17.0) for both elicitation instruments (EQ-5D and VAS), with binary dependent variable taking the value of 1 if the QoL measure increased at FU visit M12 compared to baseline, and 0 otherwise. The results of the logit model (unadjusted and adjusted) were reported in odds ratios.

3 Results

3.1 Sample characteristics

Among 542 KTR included in the EU-TRAIN trial, we received individual patient data from 491 KTR who completed at least one QoL questionnaire at initiation or baseline (Month 0 = M0), whereby the French hospitals collected information on the majority of the study sample (71%, n = 349) (Table 1). Overall, 286 KTR completed only the VAS questionnaire (273 KTR with non-missing background characteristics), 214 KTR completed only the EQ-5D questionnaire (204 with non-missing background characteristics), and 212 KTR completed both EQ-5D and VAS questionnaires.

10.3389/fphar.2023.1040584

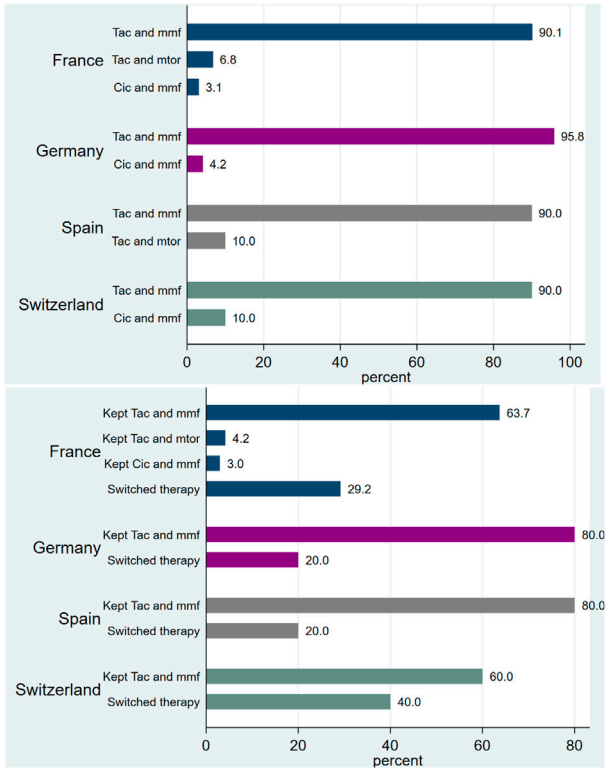

FIGURE 1
Proportion (%) of patients with immunosuppressant therapies, at baseline and at visit M12.

FIGURE 2
Mean EQ-5D scores and VAS scores by therapy type at baseline and in the last visit (trend) among only those people with non-missing EQ-5D and VAS scores (*N* = 205). *Overall mean EQ-5D score changed from 0.85 to 0.88, and mean VAS changed from 0.67 to 0.79

The mean age ranged from 55 to 61.7 years, whereby the KTR in Spain were on average of older age than in the other countries. In all nine transplantation centers, the majority of KTR were males while the proportion varied from 54% (hospital in Germany) to 86% (hospital in Spain). The vast majority of KTR had several comorbidities (84%–100%), whilst there was a larger variation in the smoking history (17%–57%) and diabetes history (3%–43%). Mean eGFR at baseline was lowest in the University hospitals of Geneva (6.6 mL/min/1.73 m^2) and highest in the Spanish centers (17.0 mL/min/1.73 m^2). BMI ranged from 24.8 kg/m^2 in France to 28.0 kg/m^2 in Spain.

The proportions of KTR receiving various immunosuppression therapies at baseline and at FU visit (M12) are detailed (Figure 1). The majority of KTR in all countries (>90%) received SOC at baseline (Tac and Mmf). However, at M12, multiple KTR switched therapies, with percentages varying from 20% in Germany and Spain to 40% in Switzerland (Figure 1).

The impact of glucocorticoids on QoL was hardly assessable because they were used in high dose during the induction phase followed by tapering dosages. Therefore, their influence on patient QoL is hardly feasible without strong assumptions: 511 (94.63%) recipients had glucocorticoids after the KT with dose tapering during the study period. Thus, 415 (92%) had still low dose prednisone 5–40 mg/d after 3 months (M3) and 391 (90%) had lower dose (5–15 mg/d) after 12 months (M12).

3.2 Quality-of-life among KTR with various immunosuppressive therapies

Mean VAS scores at baseline were systematically lower than EQ-5D scores, with total means of 0.68 VAS versus 0.85 EQ-5D: statistically significant differences existed between countries (Table 1). Overall, QoL measured by VAS and EQ-5D showed a positive trend over the period from baseline until the FU visit (M12) (Figure 2). KTR who switched therapies had lower EQ-5D and VAS scores than KTR keeping their therapies, especially in the case of EQ-5D (Figure 2). Additionally, VAS scores, although generally lower than EQ-5D, showed a larger increase over time for all therapy groups: mean EQ-5D score changed from 0.85 to 0.88, and mean VAS changed from 0.67 to 0.79.

Bivariate and multivariate analysis using generalized linear models showed that KTR who kept standard care therapy (Tac and Mmf) had significantly better EQ-5D and VAS scores at M12 than KTR in the group of therapy switchers, by eight percentage points (pp) in EQ-5D and four pp in VAS (Tables 2, 3). The analysis also indicated a trend for higher scores in KTR with therapies based on Tac, mTOR, Cic, and Mmf. Additionally, the

TABLE 2 EQ-5D at closing visit M12 and improvement of EQ-5D over the whole observation period.

	EQ-5D, average marginal effects			Improved EQ-5D, odds ratios	
	Unadj., $N = 214$	Adj. , $N = 204$		Unadj	Adj
Type of drug			Type of drug		
Switched therapy	*References*		***Cic and mmf***	*References*	
Kept Tac and mmf	0.08**	0.06*	*Tac and mmf*	0.99	0.99
Kept Tac and mtor	0.13	0.06	*Tac and mtor*	1.05	1.12
Kept Cic and mmf	0.16	0.15	**Switched therapy**	1.21	1.27
Males	—	0.07**	**Males**	—	0.75
History of diabetes	—	−0.05	**History of diabetes**	—	1.08
BMI	—	0.01**	**BMI**	—	1.01
Estimated GRF at month 12	—	0.002***	**Estimated GRF at month 12**	—	1.01

* = $p < 0.1$, ** = $p < 0.05$, *** = $p < 0.01$.
Bold are the names of the variables used in the analysis. In bold italic is the reference category from a categorical variable *Type of drug*.

TABLE 3 VAS scores at closing visit M12 and improvement of VAS score over the whole observation period.

	VAS, average marginal effects			Improved VAS, odds ratios	
	Unadj., N = 286	Adj., N = 273		Unadj	Adj
Type of drug			Type of drug		
Switched therapy	*References*		***Cic and mmf***	*References*	
Kept Tac and mmf	0.04*	0.03	*Tac and mmf*	1.41	1.09
Kept Tac and mtor	0.07	0.04	*Tac and mtor*	1.58	1.20
Kept Cic and mmf	0.05	0.05	**Switched therapy**	0.43**	0.45*
Males	—	0.02	**Males**	—	1.13
History of diabetes	—	−0.07**	**History of diabetes**	—	0.94
BMI	—	−0.00	**BMI**	—	0.98
Estimated GRF at month 12	—	0.001**	**Estimated GRF at month 12**	—	1.01*

* = $p < 0.1$, ** = $p < 0.05$, *** = $p < 0.01$.
Bold are the names of the variables used in the analysis. In bold italic is the reference category from a categorical variable *Type of drug*.

TABLE A1 95% Confidence intervals corresponding to the **Figure 2** data points.

Therapy/visit	Visit 0 EQ-5D	Visit 12 EQ-5D	Visit 0 VAS	Visit 12 VAS
Tac and Mmf	0.87 [0.84; 0.90]	0.90 [0.87; 0.93]	0.67 [0.64; 0.70]	0.79 [0.77; 0.82]
Tac and Mtor	0.91 [0.82; 1.00]	0.97 [0.92; 1.02]	0.73 [0.54; 0.92]	0.84 [0.73; 0.96]
Cic and Mmf	0.89 [0.77; 1.00]	0.97 [0.88; 1.05]	0.73 [0.52; 0.94]	0.85 [0.73; 0.97]
Switched	0.81 [0.74; 0.88]	0.82 [0.74; 0.89]	0.68 [0.64; 0.72]	0.76 [0.72; 0.80]

eGRF was positively and significantly associated with QoL measured by EQ-5D and VAS; males tended to have higher EQ-5D score than females, and the history of diabetes was associated with a worse VAS score (Tables 2, 3).

Finally, although there was overall a positive trend in QoL (Figure 2, confidence intervals are presented in Appendix Table 1), the logistic regression analysis estimating the probability of improved EQ-5D or VAS during the

TABLE A2 Improvement in raw scores (EQ-5D or VAS from baseline to visit M12, presented in odds ratios).

	EQ-5D improved		VAS improved	
	Adj. , *N* = 204	Unadj. , *N* = 214	Unadj., *N* = 286	Adj., N = 273
Type of drug				
Switched therapy	References		References	
Kept Tac and mmf	1.08	1.24	1.51	1.29
Kept Tac and mtor	0.92	0.99	1.52	1.26
Kept Cic and mmf	2.80	2.48	0.57	0.57
Males	0.67	-	-	0.97
History of diabetes	0.85	-	-	0.82
BMI	1.00	-	-	1.00
Estimated GRF at month 12	1.02**	-	-	1.01

* = $p < 0.1$, ** = $p < 0.05$, *** = $p < 0.01$.

obervational period, it did not show any significant results (Appendix Table 2). Only in specification where the effect of a therapy use was separated from the effect of switching (Tables 2, 3), the VAS score showed to be significantly worse if the KTR switched therapy during the FU period, irrespective of the immunosuppressive therapy.

4 Discussion

To our knowledge, this was the first prospective, international, multicenter study including 542 renal transplant patients that evaluated non-invasive biomarkers and immunosuppressants on PROMs. We described QoL in patients receiving immunosuppressive therapies at initiation and at (M12) and explored whether there was any improvement in QoL over the whole observation period. We found that QoL measured by VAS scores were systematically lower compared to EQ-5D and different QoL outcomes were observed at (M12) depending on the elicitation instrument (EQ-5D or VAS), and when KTR needed to switch immunosuppressants (*versus* kept standard treatment). Specifically, KTR switching therapies had lower scores in EQ-5D and VAS scores at FU visit than KTR receiving SOC (Tac and Mmf) in the first year following renal transplantation, most likely reflecting reactive changes of immunosuppressants due to adverse events. Looking at QoL improvements over the whole observation period, individuals who switched therapies were significantly less likely to improve VAS scores than non-switchers. There were no significant improvements in QoL over the observation period that was attributed to a specific treatment. Additionally, other parameters (gender, eGFR, BMI and the history of diabetes) were associated with different QoL outcomes and considered for the adjustment.

There is still a lack of common agreement regarding interpretation discrepancies between VAS ad EQ-5D values (Badia et al., 1999; Brazier et al., 2003; Lamers et al., 2006; Golicki et al., 2015). Differences in the elicitation method could provide credible explanations: the VAS provides a direct valuation of the respondent's health state, while EQ-5D descriptive system is converted into an index score using specialized country-specific population-based value set and statistical routine (Grandy and Fox, 2008). Population-based value sets used in the current study from France, Germany, and Spain (Badia et al., 2001; Greiner et al., 2005; Chevalier and de Pouvourville, 2013) used the time trade-off (TTO) technique to elicit EQ-5D health values. TTO is a choice-based measure using hypothetical scenarios, often considered more reliable and accurate for health valuation, since it characterizes health decisions and not only health states (Dolan, 2000; Craig, 2009). Thus, differential framing and eliciting method between the VAS and TTO-based EQ-5D scores may lead to observed differences in values (Craig, 2009). Empirical studies showed evidence of a weak to moderate correlation between VAS and TTO values when performed at the same time, whilst there was a strong correlation between VAS and measures of health status (e.g., pain, physical functioning or clinical symptoms) (Bakker et al., 1994; Green et al., 2000; Lamers et al., 2006).

In this study the EQ-5D scores exceeded VAS scores, which was in line with the majority of previous studies (Brazier et al., 2003; Bernert et al., 2009; Kang et al., 2014; Burstrom et al., 2020). This finding was observed earlier as a result of disproportionate point interval, reflecting a large gap between the EQ-5D-3L values attached to poorest health state (33333) and next poorest states (e.g., 33323) (Badia et al., 1999). Such a value gap may be especially prominent in our sample of patients receiving immunosuppressive therapies after kidney transplantation who are likely to indicate poorer health states. Similarly, value gaps have been reported in other settings, such as in cardiology after acute coronary syndromes (Gencer et al., 2016; Laurencet et al., 2016) and major adverse cardiovascular events associated with COVID-19 (Tessitore et al., 2021).

We acknowledge limitations inherent to these findings issued from the EU-TRAIN cohort study. First, because of the observational nature of the study, the results did not provide any causal inference. This is particularly true if someone assumes that untoward evolution of a renal transplant might be associated with changes in immunosuppressive therapies that would fail to improve renal function or graft survival. Second, possibly for cultural reasons, the proportions of fully completed

questionnaires differed significantly across centers: missing data were more frequent in Spain than in other centers. We also lacked background information about non-responders to identify any clue regarding response biases. Third, some initial therapeutic combinations are overrepresented (>90% of RTR took Tac + Mmf) and appeared to perform better according to EQ-5D: again, no inference could done be since patient selection bias could not be excluded (transplant patients will remain on initial therapy if the evolution is favorable). Fourth, in spite of mandatory therapeutic drug monitoring (TDM) requirements, the formal adherence to treatment (compliance) has not been assessed, e.g. using specific elicitation methods, such as the validated Basel assessment of adherence to immunosuppressive medications scale (BAASIS®) in kidney transplants (Marsicano et al., 2013). TDM data were not sufficiently detailed to assess medication compliance deviations (i.e., detailed blood sampling time with respect to drug intakes).

Strengths of the study are new insights into a wide range of medical management aspects based on PROMs, including adaptation of immunosuppressant therapy that could not be driven by laboratory parameters. Despite the initial SOC were comparable, patient characteristics and evolving trends differed across countries more than between centers. In addition, the statistical model was adjusted taking into account relevant parameters, such as the medical history and residual renal function that impacted significantly on the QoL and related health utility indexes. Finally, in line with previous studies on PROMs, we could provide evidence that VAS and EQ-5D are complementary instruments that delivered sound estimates for multidimensional FU and QoL: both elicitation methods discriminated various therapeutic outcomes, if adjusted for medical history and patient characteristics.

Future perspectives include the investigation on whether actionable data analytics could promote efficient IKR monitoring with less invasive procedures: targeted allograft protocol biopsies to predict allograft rejection based on a series of non-invasive biomarkers and other predictors are expected to facilitate patient FU, increase QoL, and reduce procedural costs.

Undoubtedly, the involvement of PROMs becomes an integral part of international cohort studies to issue recommendations in addition to clinical outcomes. Furthermore, health technology assessment (HTA) could be carried out as ancillary analisis through the development of decision models (Markov modelling, Monte-Carlo simulations, and probabilistic sensitivity analyses) to extrapolate expected effects over longer time-horizons than trials.

Beyond clinical and health economic aspects, this preliminary study lays the groundwork for future analytical frameworks to streamline pivot decision and innovation in transplantation medicine and nephrology. We expect that, on the long-term, findings derived from PROMs will help clinicians, public health authorities, and policymakers to take informed decision when revising guidance in renal transplantation standards and immunosuppression protocols.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Local ethics committee in Berlin, Paris, Nantes, Geneva and Barcelona, on behalf of the EU-TRAIN Consortium. The patients/participants provided their written informed consent to participate in this study.

Author contributions

FG: Conceptualization, methodology, supervision, writing—original draft preparation, writing—reviewing and editing, funding acquisition, project administration. AN: Formal analysis, software, writing—original draft preparation, visualization, investigation, writing—reviewing and editing; OB, CL, KB, FH, SB, MG, P-AG, and JV: Patient inclusion, investigation, reviewing, and funding acquisition. BH: Data management and data extractions. JM: Conceptualization, methodology, supervision, writing—reviewing and editing. AL: Project administration, supervision, reviewing, and funding acquisition.

Funding

The project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 754995. Open access funding by University of Lausanne.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Badia, X., Monserrat, S., Roset, M., and Herdman, M. (1999). Feasibility, validity and test-retest reliability of scaling methods for health states: The visual analogue scale and the time trade-off. *Qual. Life Res.* 8, 303–310. doi:10.1023/a:1008952423122

Badia, X., Roset, M., Herdman, M., and Kind, P. (2001). A comparison of United Kingdom and Spanish general population time trade-off values for EQ-5D health states. *Med. Decis. Mak.* 21, 7–16. doi:10.1177/0272989X0102100102

Bakker, C., Rutten, M., Vandoorslaer, E., Bennett, K., and Vanderlinden, S. (1994). Feasibility of utility-assessment by rating-scale and standard gamble in patients with ankylosing-spondylitis or fibromyalgia. *J. Rheumatology* 21, 269–274.

Bernert, S., Fernandez, A., Haro, J. M., Konig, H. H., Alonso, J., Vilagut, G., et al. (2009). Comparison of different valuation methods for population health status measured by the EQ-5D in three European countries. *Value Health* 12, 750–758. doi:10.1111/j.1524-4733.2009.00509.x

Brazier, J., Green, C., Mccabe, C., and Stevens, K. (2003). Use of visual analog scales in economic evaluation. *Expert Rev. Pharmacoecon Outcomes Res.* 3, 293–302. doi:10.1586/14737167.3.3.293

Burstrom, K., Teni, F. S., Gerdtham, U. G., Leidl, R., Helgesson, G., Rolfson, O., et al. (2020). Experience-based Swedish TTO and VAS value sets for EQ-5D-5L health states. *Pharmacoeconomics* 38, 839–856. doi:10.1007/s40273-020-00905-7

Chevalier, J., and De Pouvourville, G. (2013). Valuing EQ-5D using time trade-off in France. *Eur. J. Health Econ.* 14, 57–66. doi:10.1007/s10198-011-0351-x

Chong, K., Myaskovsky, L., and Unruh, M. (2018). A timely evaluation of the psychometric properties of the KDQOL-36. *Am. J. Kidney Dis.* 71, 449–451. doi:10.1053/j.ajkd.2017.10.028

Craig, B. M. (2009). The duration effect: A link between TTO and VAS values. *Health Econ.* 18, 217–225. doi:10.1002/hec.1356

Dolan, P. (1997). Modeling valuations for EuroQol health states. *Med. Care* 35, 1095–1108. doi:10.1097/00005650-199711000-00002

Dolan, P. (2000). "The measurement of health-related quality of life," in *Handbook of health economics*. Editors A. J. Culyer and J. P. Newhouse (Amsterdam, Netherlands: Elsevier Science B.V).

Gencer, B., Rodondi, N., Auer, R., Nanchen, D., Raber, L., Klingenberg, R., et al. (2016). Health utility indexes in patients with acute coronary syndromes. *Open Heart* 3, 419. doi:10.1136/openhrt-2016-000419

Golicki, D., Niewada, M., Karlinska, A., Buczek, J., Kobayashi, A., Janssen, M. F., et al. (2015). Comparing responsiveness of the EQ-5D-5L, EQ-5D-3L and EQ VAS in stroke patients. *Qual. Life Res.* 24, 1555–1563. doi:10.1007/s11136-014-0873-7

Grandy, S., and Fox, K. M. (2008). EQ-5D visual analog scale and utility index values in individuals with diabetes and at risk for diabetes: Findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). *Health Qual. Life Outcomes* 6, 18. doi:10.1186/1477-7525-6-18

Green, C., Brazier, J., and Deverill, M. (2000). Valuing health-related quality of life - a review of health state valuation techniques. *Pharmacoeconomics* 17, 151–165. doi:10.2165/00019053-200017020-00004

Greiner, W., Claes, C., Busschbach, J. J., and Von Der Schulenburg, J. M. (2005). Validating the EQ-5D with time trade off for the German population. *Eur. J. Health Econ.* 6, 124–130. doi:10.1007/s10198-004-0264-z

Iaria, G., Anselmo, A., De Luca, L., Manuelli, M., Lucchesi, C., Tariciotti, L., et al. (2007). Conversion to rapamycin immunosuppression for malignancy after kidney transplantation: Case reports. *Transplant. Proc.* 39, 2036–2037. doi:10.1016/j.transproceed.2007.05.046

Kang, H. J., Kang, E., Jo, M. W., Park, E. J., Yoon, S., and Lee, E. K. (2014). The utility score of epilepsy with partial seizure measured by TTO, VAS, and EQ-5D in the general Korean population. *Epilepsy Res.* 108, 963–971. doi:10.1016/j.eplepsyres.2014.02.014

Kim, J., and Jang, I. (2020). Validation and adaptation of the "modified transplant symptom occurrence and symptom distress scale" for kidney transplant recipients. *Int. J. Environ. Res. Public Health* 17, 7348. doi:10.3390/ijerph17197348

Kullberg, E. B., Noble, C., Odisho, A., Drummond, D., Kirpotin, D., Zhou, E. Y., et al. (2005). Multitargeted immunoliposomes for cancer therapy. *Clin. Cancer Res.* 11, 9004s.

Lamers, L. M., Stalmeier, P. F., Krabbe, P. F., and Busschbach, J. J. (2006). Inconsistencies in TTO and VAS values for EQ-5D health states. *Med. Decis. Mak.* 26, 173–181. doi:10.1177/0272989X06286480

Laurencet, M. E., Girardin, F., Rigamonti, F., Bevand, A., Meyer, P., Carballo, D., et al. (2016). Early discharge in low-risk patients hospitalized for acute coronary syndromes: Feasibility, safety and reasons for prolonged length of stay. *PLoS One* 11, 161493. doi:10.1371/journal.pone.0161493

Marsicano, E. D., Fernandes, N. D., Colugnati, F., Grincenkov, F. R. D., Fernandes, N. M. D., De Geest, S., et al. (2013). Transcultural adaptation and initial validation of Brazilian-Portuguese version of the Basel assessment of adherence to immunosuppressive medications scale (BAASIS) in kidney transplants. *Bmc Nephrol.* 14, 108. doi:10.1186/1471-2369-14-108

Rabin, R., and De Charro, F. (2001). EQ-5D: A measure of health status from the EuroQol group. *Ann. Med.* 33, 337–343. doi:10.3109/07853890109002087

Rabin, R., Gudex, C., Selai, C., and Herdman, M. (2014). From translation to version management: A history and review of methods for the cultural adaptation of the EuroQol five-dimensional questionnaire. *Value Health* 17, 70–76. doi:10.1016/j.jval.2013.10.006

Tessitore, E., Handgraaf, S., Poncet, A., Achard, M., Hofer, S., Carballo, S., et al. (2021). Symptoms and quality of life at 1-year follow up of patients discharged after an acute COVID-19 episode. *Swiss Med. Wkly.* 151, 30093. doi:10.4414/smw.2021.w30093

Frontiers in Pharmacology

Explores the interactions between chemicals and living beings

The most cited journal in its field, which advances access to pharmacological discoveries to prevent and treat human disease.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact