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Value-based healthcare in oncology

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Value-based healthcare in oncology

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Editorial: Value-based healthcare in oncology

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value-based, healthcare, cancer, public health, patient centeredness

Editorial on the Research Topic
Value-based healthcare in oncology

Value in Healthcare, defined as the relationship between outcomes and costs (1), including direct financial costs and indirect costs such as impact on employment, treatment toxicity, and family/caregiver impact, remains a complex and multifaceted concept. Value-based healthcare is of primary importance in oncology as, over the past decades, neoplastic diseases have increased in incidence and prevalence, becoming one of the leading causes of death.

The objective of this Research Topic was to contribute to the existing body of knowledge with a clear picture of the current scenario of the Value-Based approach in oncologic clinical practice to deliver sound experience on its impact, potential benefits, challenges to address, and future research needs.

A total of 21 manuscripts were submitted, eleven of which were accepted.

Most of the contributions aimed at evaluating the economic efficacy or the financial impact of single/combined treatments of cancer diseases with a particular public health burden.

In other cases, authors shared the results of their research on the impacts of the application of effective models of value-based care (Bigi et al.); they analyzed a new tool to combine reported quality experiences and patient-reported outcomes (de Mattia et al.).

Also, organizational and financing implications from reshaping the delivery of healthcare services according to a Value-Based care approach have been published. For example, studies on the experience of involving patients and professionals in a co-constructed therapeutic pathway (Casà et al.); a Value-Based approach to untangle the full benefit of HPV-related cancers elimination strategies and identify priority and best practices (Calabrò et al.) have been reported, respectively.

Value-based healthcare in oncology still has some limits, as there remains no standard to quantify the many outcomes and cost components of value (i.e., patient-reported outcomes and estimated costs to patients), thus various conceptual frameworks have been proposed (2).

Furthermore, publishing has become more and more challenging and there are several reasons for the difficulties. I have encountered as an Editor that as a Public Health journal we cannot simply store papers that arrive spontaneously (even after a qualitative selection), and we tried to orient publishing according to validity, rigor, and relevance (3).

We also tried to challenge the public health research community to address future research needs, such as refinement of performance indicators to include patients' perspective (PROMS/PREMS); implementation of shared decision-making as routine in clinical

practice; reshaping of logistics and operations to respect the values of "green" care delivery; digital support for the implementation of Value-Based approaches; reshaping of reimbursement systems to bundled payments based on clinical outcomes.

Indeed, we received a few feedbacks on some of these items.

Thus, from a public health perspective and by considering the great expansion of the research community, particularly from emerging countries and low-income countries, it will be crucial for healthcare organizations to use *Value-based healthcare in oncology* to improve the quality of care on an individual level and consider patients' concerns and needs; reduce unwarranted duplications and wastes in care provision via more regular or systematic assessment of the effectiveness of care and monitoring of disease progression; increase patient information, communication, and shared medical decision-making, thus paving the way for precision and personalized medicine.

Author contributions

AB: Writing—original draft, Writing—review and editing.

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Conflict of interest

The author declares 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

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ORIGINAL RESEARCH
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Cost-Effectiveness Analysis of a Three-Drug Regimen Containing Bevacizumab for the Treatment of Recurrent Pediatric *Medulloblastoma* in China: Based on a COG Randomized Phase II Screening Trial

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Background: *Medulloblastoma* is the most common malignant brain tumor of childhood, accounting for 6 to 7 percent of all childhood CNS tumors. The purpose of this study was to evaluate the economic efficacy of a bevacizumab combined with *temozolomide* + irinotecan regimen for the treatment of recurrent pediatric *medulloblastoma* in China.

Methods: The data analyzed were from a randomized phase II screening trial that showed an improved survival benefit in child patients with recurrent *medulloblastoma* treated with a T+I+B combination regimen. A Markov model is constructed to estimate the incremental cost–effectiveness ratio (ICER) from the perspective of Chinese society. The uncertainty in the model is solved by one-way certainty and probabilistic sensitivity analysis.

Results: Our base case analysis showed that the total costs of treatment increased from $8,786.403 to $27,603.420 with the combination bevacizumab vs. the two-agent chemotherapy regimen. Treatment with T+I+B combination therapy was associated with an increase in effectiveness of 0.280 QALYs from 0.867 to 1.147 QALYs T+I regimen. The incremental cost-effectiveness ratio was $67,203.632/QALY, which exceeded our pre-specified willingness-to-pay threshold ($38,136.26/QALY). Cost changes associated with grade 3–4 AE management, tests used, or hospitalization costs had little effect on the ICER values predicted by sensitivity analysis.

Conclusions: Taken together, the results of this study suggest that the combination of bevacizumab with temozolomide and irinotecan is not a cost-effective option from the perspective of Chinese payers as a first-line treatment option for children with recurrent *medulloblastoma* in China.

Keywords: recurrent pediatric *medulloblastoma*, bevacizumab, *temozolomide*, irinotecan, cost-effectiveness

INTRODUCTION

Medulloblastoma is the most common malignant brain tumor of childhood, accounting for 6 to 7 percent of all childhood CNS tumors (malignant and non-malignant) (1), and occurs in the posterior fossa, mainly in the cerebellum. Most patients are treated with a combination of surgery, radiation therapy (RT), and chemotherapy. Currently, approximately three-quarters of patients survive for a long time, but each treatment modality leads to late complications, which have a great impact on the quality of life of patients. In a retrospective study of 1,485 children with primary CNS tumors who attended a neurosurgery center in China between 2001 and 2005, *medulloblastoma* was ranked third among the top five most common brain tumors (2).

Approximately 30% of children with MB will relapse after aggressive treatment, including surgery and chemotherapy, with or without radiation. Treatment options for recurrent *medulloblastoma* are still controversial and lack standards (3, 4). Tumor-targeted therapy at relapse appears to improve overall survival (OS) compared with palliative care alone, but long-term survival remains below 10% in most studies. Therefore, the results of this largest cohort study to date shed new light on regimen options for children with recurrent *medulloblastoma* (5). The study showed that bevacizumab combined with *temozolomide* + irinotecan regimen can significantly prolong event-free survival and overall survival in children and improve prognosis.

Although bevacizumab combination therapy is effective and well tolerated in children with recurrent *medulloblastoma*, the high cost of these drugs must be considered. These high costs can have profound effects on patients in the form of financial toxicity, causing patients to abandon or delay care, reduce quality of life, and put patients at risk of bankruptcy. From a social point of view, as a country with a large population, China has relatively underdeveloped medical resources, unbalanced regional economic development, and large differences in local medical insurance policies. In recent years, the national oncology drug negotiation agenda has been increasingly advanced, and the pricing of many drugs has undergone great changes. Few studies have examined the economics of bevacizumab in children with recurrent *medulloblastoma*. Therefore, in this context, our study uses the Markov model to evaluate the economics of the T+I+B scheme in China, aiming to provide necessary reference and data support for doctors, patients and policy makers.

MATERIALS AND METHODS

Target Population

Inclusion criteria included patients under the age of 21 who relapsed or were refractory to standard chemotherapy, and the number of relapses was fixed at 1–2. All had a histological diagnosis prior to enrollment, and residual disease was defined as tumor measurable on MRI in two perpendicular diameters. Organ function was also assessed. Enrolled patients were randomized to receive either a two-drug regimen including temozolomide (TMZ, 50 mg/m^2 PO for 5 days) plus irinotecan (IRT, 50 mg/m^2 IV for 5 days) or TMZ, IRT plus bevacizumab (BEV, 10 mg/kg IV on days 1 and 15). The regimen was repeated every 28 days for a maximum of 12 courses until intolerable toxicity or disease progression.

Model Structure

Patients enter the Markov model in a stable disease state, and then they may remain in a stable disease state (event-free survival, EFS) or experience toxic effects, disease progression (PD), or death (**Figure 1**). The transition probabilities for these events were derived from COG data. We extracted progression and survival data from reported Kaplan–Meier curves. Similar to previous cost-effectiveness studies, we only included and assessed grade 3 to 4 treatment-related adverse events. Toxicity was defined using the National Cancer Institute Common Toxicity Criteria (version 3.0). According to the survival and follow-up time, we set the model period to be 1 month. We reconstructed individual patient data through R software, and the transition probability was estimated through the reported survival curve. The standard for setting the running time of the model is that 99% of patients enter the termination state. The time horizon chosen for this model is 10 years.

Model Parameters

Costs are estimated from the perspective of Chinese society (**Table 1**). The following costs were considered during the analysis: all medications, tests (MRI, biochemistry, etc.), management of grade 3–4 adverse events (AEs), and hospitalization. In view of the fact that hidden costs are often difficult to be accurately counted in real life, and there are large individual differences, the hidden costs of this study were not included in the calculation. For the drug dose parameters,

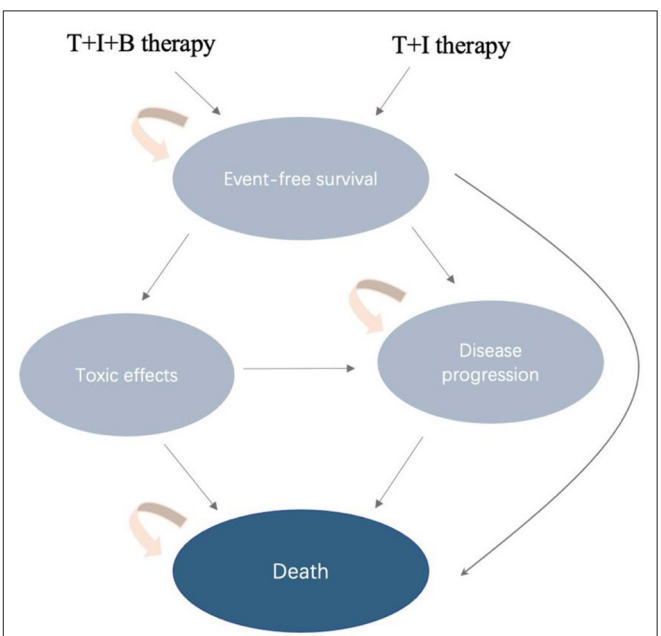

FIGURE 1 | Diagram of transitions between health states.

TABLE 1 | Parameters for the base case cost-effectiveness model.

Parameters	Value	Distribution	Source
Clinical efficacy, months			
Median EFS			
T+I+B	9	Weibull	(5)
T+I	6	Weibull	(5)
Median OS			
T+I+B	19	Weibull	(5)
T+I	13	Weibull	(5)
Drug costs per cycle, $			
Conbination T+I+B	2803.73	Gamma	Listed price
Conbination T+I	919.90	Gamma	Listed price
Temozolomide in T+I+B regimen	343.75	Gamma	Listed price
Irinotecan in T+I+B regimen	576.15	Gamma	Listed price
Bevacizumab	1,883.83	Gamma	Listed price
Temozolomide in T+I regimen	343.75	Gamma	Listed price
Irinotecan in T+I regimen	576.15	Gamma	Listed price
Second-line treatment in T+I+B regimen	233.11	Gamma	(6)
Second-line treatment in T+I regimen	305.67	Gamma	(6)
Hospitalization costs in T+I+B regimen	43.96	Gamma	HIS
Hospitalization costs in T+I regimen	43.96	Gamma	HIS
Drug toxic effects costs, $			
T+I+B	10.09	Gamma	(5), Listed price
T+I	13.87	Gamma	(5), Listed price
Tests costs per cycle, $			
T+I+B	185.63	Gamma	(5), HIS
T+I	176.56	Gamma	(5), HIS
Disease costs per cycle, $			
Event-free survival in T+I+B	3,043.40	Gamma	Listed price, HIS
Event-free survival in T+I	1,154.28	Gamma	Listed price, HIS
Disease status utility per year, QALY			
Event-free survival	0.89	Beta	(7)
Progressed disease	0.73	Beta	(7)
Death	0.00	Beta	(7)
Discount rate, %	3.00	Beta	(8)

HIS, Hospital Information System; EFS, Event-free Survival; OS, Overall Survival; T, Temozolomide; I, Irinotecan; B, Bevacizumab; QALY, Quality-Adjusted Life Year.

we used the weighted average method to estimate height and weight with reference to the latest survey results of Chinese children (9). The formula for calculating the body surface area (BSA) of children is BSA(m^2) = 1.05+ [body weight (kg) – 30(kg)] 0.02(m^2). The unit price of each drug and examination is based on the 2022 charging standard of West China Hospital of Sichuan University and the winning bid price in the market. We estimated the cost of second-line treatment for both groups of patients based on survival data reported in the trial by Leary et al. (6). All fees are converted at RMB 6.437 per USD (March 2022). Health outcome data in this model were obtained from a randomized, controlled study. Survival time was expressed in quality-adjusted life years (QALY). Since basic information on utility value was not mentioned in the original literature, health utility value was referred to in published studies (7). Utility values for event-free survival, disease progression, and death status were 0.89, 0.73, and 0.00, respectively. The model parameters related to cost and benefit are shown in **Table 1**. According to the recommendations of the 2020 China Pharmacoeconomic Evaluation Guidelines and the Handbook (8), the cost and utility values were discounted at an annual discount rate of 3%, and a sensitivity analysis was performed.

Statistical Analysis

Cost-effectiveness was measured using an incremental cost-effectiveness ratio (ICER), which is the ratio of the differences in cost (measured in US dollars) and effectiveness (measured in QALYs) between the 2 treatments. We adopted a willingness-to-pay threshold of 3 times China's GDP per capita ($38,136.26 per QALY), which is considered cost-effective if ICERs are below $38,136.26 per QALY. We performed 1-way deterministic sensitivity analyses of each variable in the model to evaluate which variables had the greatest consequences for cost-effectiveness. The variation range of the unit price of the drug

refers to the winning price of the drug announced on the official websites of different provinces and cities. To further assess model uncertainty, we performed a probabilistic sensitivity analysis using a Monte Carlo simulation with 1,000 repetitions, allowing us to simultaneously vary uncertainty in cost, health utilities, and transition probabilities.

RESULTS

Base-Case Analysis

Our base case analysis showed that the total costs of treatment increased from $8,786.403 to $27,603.420 with the combination bevacizumab vs. the two-agent chemotherapy regimen. Treatment with T+I+B combination therapy was associated with an increase in effectiveness of 0.280 QALYs from 0.867 to 1.147 QALYs T+I regimen. The incremental cost-effectiveness ratio was $67,203.632/QALY, which exceeded our pre-specified willingness-to-pay threshold ($38,136.26/QALY) (**Figure 2**, **Table 2**). Considering the increased total cost, combination therapy with *temozolomide*, irinotecan, and bevacizumab is not an economical treatment option for children with recurrent *medulloblastoma* unless there is an appropriate grant program and health insurance policy support.

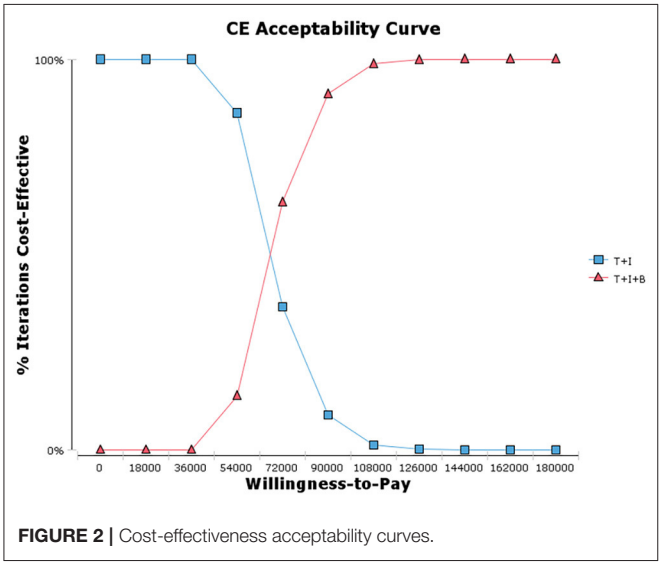

FIGURE 2 | Cost-effectiveness acceptability curves.

TABLE 2 | The results of the cost-effectiveness analysis.

Parameters	T+I+B	T+I
cEFS	25,598.444	6,543.936
cPD	2,004.976	2,242.467
uEFS	0.624	0.421
uPD	0.523	0.446
Total costs	27,603.420	8,786.403
Total effectiveness	1.147	0.867
Incremental costs	18,817.017	/
Incremental effectiveness	0.280	/
Total C/E	24,065.754	10,134.260
ICER $/QALY	67,203.632	/

Sensitivity Analysis

One-way sensitivity analysis was conducted to assess the impact of individual parameters in the Markov model. The results are illustrated using a tornado diagram (**Figure 3**). The costs of EFS state for the T+I+B group, costs of bevacizumab, and costs of irinotecan in the T+I+B group were the most influential parameters of the Markov model. In a univariate sensitivity analysis, the three-drug combination only decreased when the monthly drug cost of BEV decreased from $1,883.83 to $916.19 (a 51.4% reduction) or when the monthly combined cost of EFS status decreased from $3,042.40 to $2,075.60 (a 31.7% reduction). The T+I+B treatment regimen became economical at a willingness-to-pay threshold of $38,136.26/QALY. However, variations in the costs related to the management of grade 3–4 AEs, tests used or hospital fees incurred had a smaller impact on the ICER values predicted by sensitivity analysis. Additionally, probabilistic sensitivity analysis (1,000 iterations) demonstrated that the ICER was consistently greater than $38,136.26/QALY (**Figure 4**).

DISCUSSION

In this cost-effectiveness study, we found that bevacizumab combination therapy cannot be considered a cost-effective first-line regimen for children with recurrent *medulloblastoma* compared with dual-agent chemotherapy. Our model is not particularly sensitive to hospitalization costs or treatment costs for toxic effects. Notably, our model found that only when the monthly drug cost of BEV decreased from $1,883.83 to $916.19 (a 51.4% reduction) or when the monthly combined cost of EFS status decreased from $3,042.40 to $2,075.60 (a 31.7% reduction). The T+I+B treatment regimen became economical at a willingness-to-pay threshold of $38,136.26/QALY.

Cost-effectiveness analysis of bevacizumab for various types of brain tumors has been reported. In an economic review of bevacizumab for first-line treatment of newly diagnosed glioblastoma multiforme, the addition of bevacizumab to radiation therapy and temozolomide resulted in 0.13 quality-adjusted life years (QALY), and patients with an $80,000 increase in treatment cost over a 2-years time frame had a 0% probability of being cost-effective at a willingness-to-pay threshold of $100,000/QALY (10). In addition, bevacizumab has also shown some efficacy in metastatic solid tumors. A study of metastatic colorectal cancer in the United States showed that the total cost of capecitabine and bevacizumab needs to be reduced from $6,173 to $452, and it would be cost-effective at the willingness-to-pay threshold at the median US household income ($59,039/QALY) (11). In 2021, bevacizumab and atezolizumab significantly improved progression-free survival (PFS) and overall survival in patients with liver cancer in the IMbrave 150 trial compared with sorafenib alone. Total utility has increased by 0.53QALY, but its economics have not been shown in either China (WTP = $28,527.00/QALY) or the US (WTP = $150,000.00/QALY) market environments.

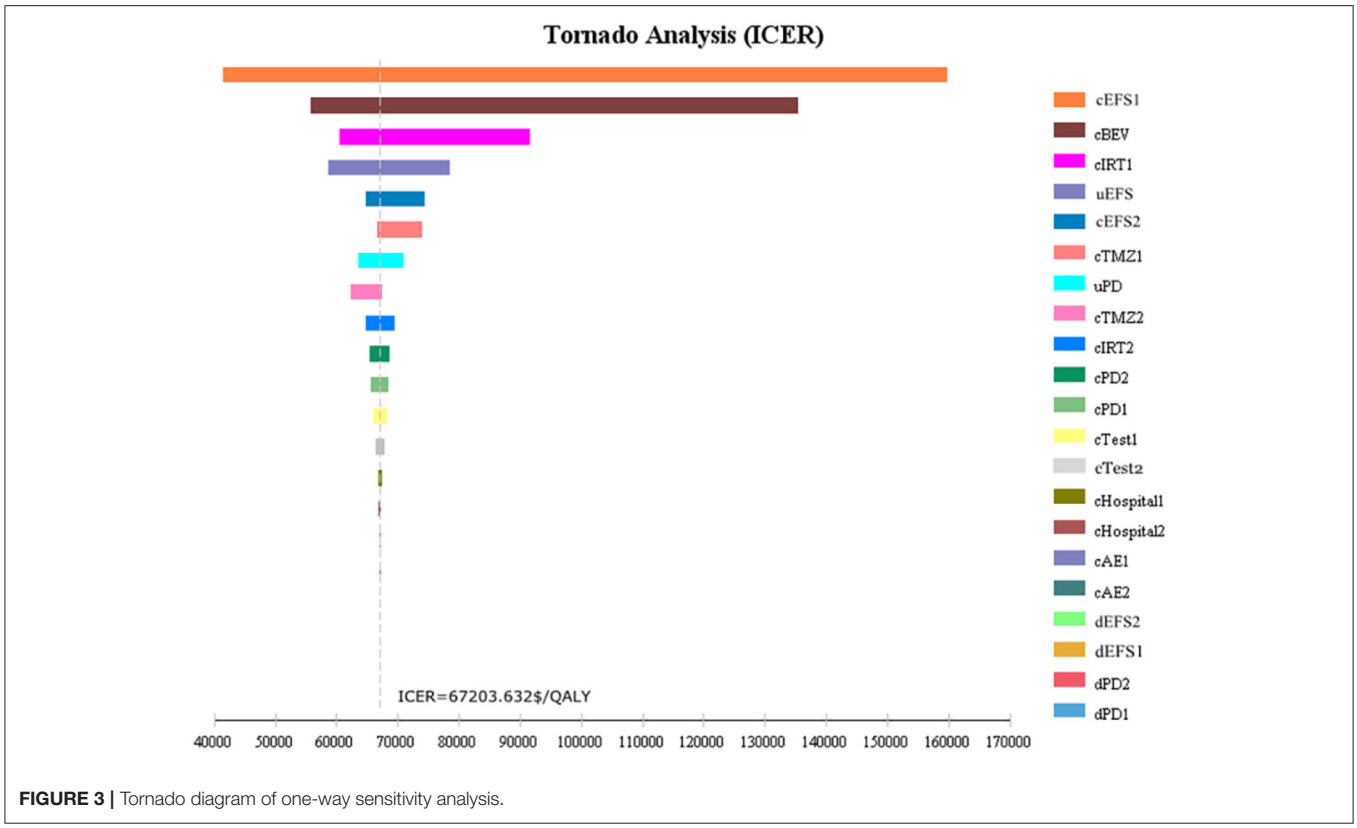

FIGURE 3 | Tornado diagram of one-way sensitivity analysis.

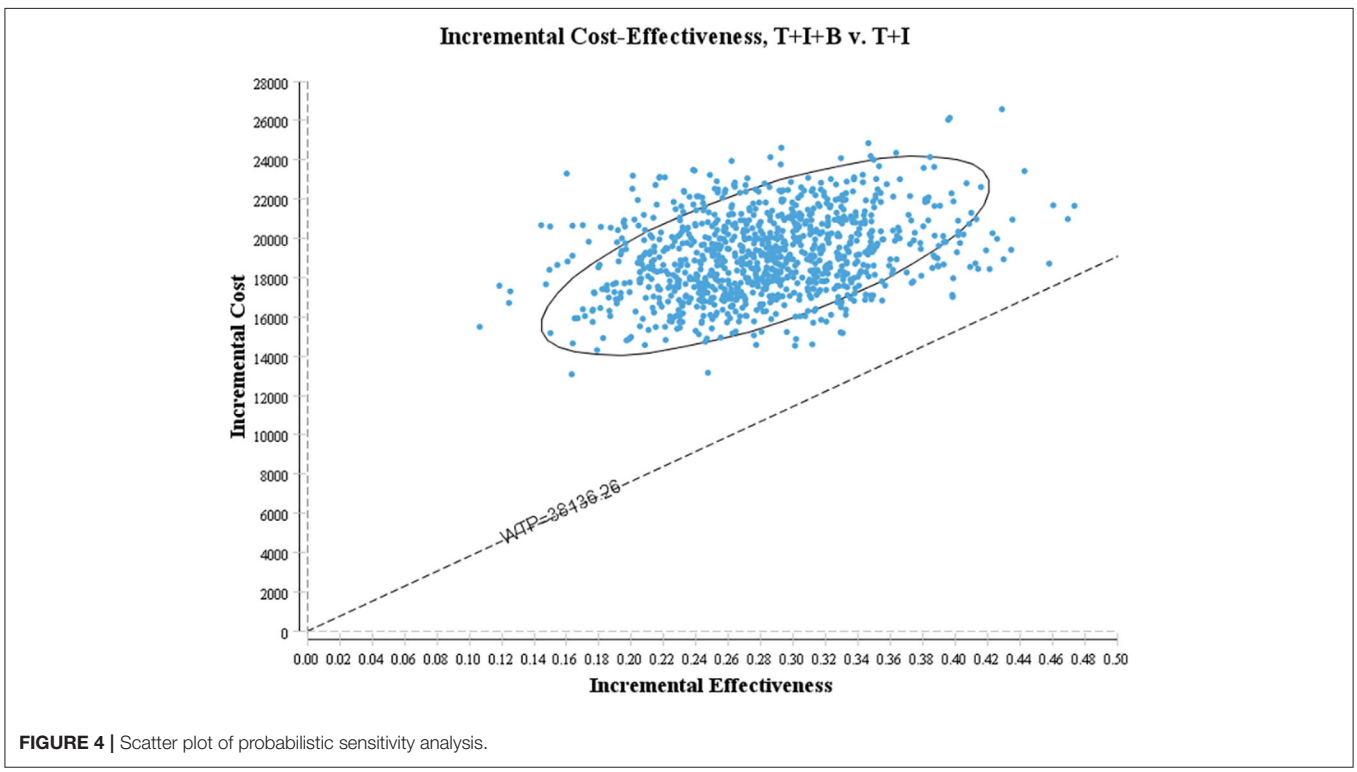

FIGURE 4 | Scatter plot of probabilistic sensitivity analysis.

Bevacizumab is an anti-vascular endothelial growth factor humanized recombinant monoclonal IgG1 antibody that was approved by the US FDA in 2007. Its mechanism is to block the binding of vascular endothelial growth factor to its receptors and inhibit the promotion of vascular endothelial growth factor. Generate activity, thereby exerting an

antitumor effect (12). In recent years, it has been found that bevacizumab may weaken the resistance of tumors to traditional chemotherapeutic drugs. The main reasons include increasing the blood concentration of chemotherapeutic drugs, prolonging the half-life of chemotherapeutic drugs, reducing the pressure of tumor interstitial fluid, and facilitating chemotherapeutic drugs to reach the tumor site (13). However, there are few large multicenter randomized controlled studies on bevacizumab in children's brain tumors. Adam et al. found that bevacizumab combined with temozolomide and irinotecan can significantly prolong the treatment of children with 8 years of follow-up. The event-free survival time and overall survival time of 10 years through the Markov model showed that the total utility increased by 0.28QALY, but it also brought a total increase of $18,817.017/person in treatment costs.

We considered the dose difference between children of different races in the model design and converted it through the body surface area formula. Toxicity profiles were comparable in both treatment arms in the trial. We still considered the cost of drug toxicity treatment. In view of the unclear social division of labor among children, the cost of lost work is not included in the calculation. It is worth noting that, as a developing country, China has a vast territory, uneven regional development, and a large economic gap between coastal and inland economies. With the advancement of medical and health reform, tumor drugs frequently appear in the national medical insurance negotiation catalog, and drug prices fluctuate greatly. Therefore, we investigated the winning bid prices in representative areas of China, east, west, north and south, and included the median in the sensitivity analysis to evaluate the stability of the model.

Univariate sensitivity analysis found that the cost of EFS status in the T+I+B group and the cost of bevacizumab and irinotecan in the T+I+B group were the most influential parameters of the Markov model. The three-drug combination decreased only when the monthly drug cost for BEV decreased from $1,883.83 to $916.19 (51.4% decrease) or the combined monthly cost for EFS status decreased from $3,042.40 to $2,075.60 (31.7% decrease). The T+I+B regimen became economical at a willingness-to-pay threshold of $38,136.26/QALY.

Our study developed a Markov decision tree model to simulate the process of disease. However, the following limitations still exist: the cost–benefit analysis model is based on phase II clinical trials rather than real-world studies, and the extrapolation of the data has certain limitations; given the lack of reporting of the original study data, the transition probability was estimated, although it has been carried out. We have conducted a single factor sensitivity analysis on the model parameters, but we do not rule out other factors that affect the model. Since the original study did not report the health utility value of children in different disease states, we refer to the published literature related to brain tumors.

Taken together, the results of this study suggest that the combination of bevacizumab with *temozolomide* and irinotecan is not a cost-effective option from the perspective of Chinese payers as a first-line treatment option for children with recurrent *medulloblastoma* in China. However, appropriate drug donation programs and social assistance should be encouraged to make this rare patient population more affordable and improve quality of life.

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/s.

AUTHOR CONTRIBUTIONS

ZC conceived and designed the experiments, wrote the manuscript, and revised the work critically for important intellectual content. ZC and FT performed the experiments and data analysis. XC and FT provided the reagents, materials and analysis tools. All authors have read and approved the final version of the manuscript.

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The value of surgical admissions for malignant uterine cancer. A comparative analysis of robotic, laparoscopic, and laparotomy surgery in a university hospital

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Background: Robotic surgery for malignant uterine cancer raises issue of economic sustainability for providers. The objective of this study was to assess the value of surgical admissions for malignant uterine cancer in a University Hospital through an analysis of their costs and outcomes by comparing three different surgical approaches (laparotomy, laparoscopic, and robotic surgery).

Methods: Hospitalizations between 1 January 2019 and 31 October 2021 for malignant uterine cancer surgery were selected and stratified. For each surgical approach, mean values (with 95% confidence intervals, CI) were calculated for cost items. Moreover, 30-day readmission frequency was calculated for the three approaches compared to each other. ANOVA and Student's *t*-test and relative risk (RR) were used for statistical analysis. A break-even analysis was carried out by evaluating the volume of robotic and non-robotic surgical admissions.

Results: A total of 1,336 hospitalizations were included in the study, 366 with robotic, 591 with laparoscopic, and 379 with laparotomy surgery. Robotic surgery, compared to laparoscopic and laparotomy ones, showed a statistically significant difference *($p < 0.001$)* in the economic margin, which was largely negative (−1069.18 €; 95%CI:−1240.44-−897.92 €) mainly due to devices cost, and a lower percentage of 30-day readmissions (1.4%; 95%CI: 0.2–2.6%), with a statistically significant difference only vs. laparotomy *($p = 0.029$)*. Laparoscopic compared to laparotomy surgery showed a significantly *($p < 0,001$)* more profitable economic margin (1692.21 €; 95%CI: 1531.75 €−1852.66 €) without a significant difference for 30-day readmissions. Break-even analysis showed that, on average, for each malignant uterine cancer elective surgery performed laparoscopically, 1.58 elective robotic surgeries are sustainable for the hospital (95% CI: 1.23–2.06).

Conclusion: Break-even analysis could be a useful tool to support hospital management in planning and governance of malignant uterine cancer surgery. Systematic application of this tool will allow defining over time right distribution of robotic, laparoscopic, and laparotomy surgeries' volumes to perform to ensure both quality and economic-financial balance and therefore value of uterine oncological surgery. Concerning research, this study paves the way for a multicentric study, the extension of outcomes of malignant uterine surgery to be considered and assessed, and the future inclusion of other therapeutic interventions in the analysis.

KEYWORDS

value-based healthcare, oncology, public health, healthcare system, robotic

Introduction

In the early 1990s, the need to move away from a purely volume-driven system in favor of a more value-driven one began to emerge in the area of health services management. This meant focusing more on the quality of care than its volume (1).

The focus on value-driven healthcare increased in 2006 when Porter and Teisberg introduced the concept of value-based healthcare (VBHC), a new strategy for delivering and measuring healthcare (2–4).

The constitutive element of the VBHC concept is that value is defined as the measured improvement in a patient's health outcomes for the cost of achieving that improvement. The value can be increased by lowering healthcare costs or improving care outcomes, or both (1).

The foundational element of VBHC is the concept of measurement: On the one hand, the ultimate goal of healthcare is to improve the health status of the patient, but on the other hand, it is necessary to stay within certain spending limits. Therefore, in a value-based analysis, it is essential to measure both outcomes and costs of individual patient care processes. The results from these analyses allow us to understand whether they are doing well and where to improve in terms of care and efficiency (5).

This approach has found widespread success in modern healthcare management (1), and value dimensions are widely represented among the performance dimensions in hospital care (6).

The value-performance approach can find effective application in oncological surgery of malignant neoplasms of the uterus whose costs and outcomes have been reported in the scientific literature (7–10).

Indeed, endometrial cancer for instance is the most common gynecologic malignancy in developed countries and among most frequent women's cancers, with 8300 estimated cases in 2020 and 3100 estimated deaths in 2021 in Italy. Cervical cancer also plays an important role in terms of disease burden with 2400 cases in 2020 among women in Italy (11, 12).

These simple epidemiological data make uterine neoplastic diseases a focal element on which to concentrate modern therapeutic efforts (13, 14).

The standard treatment of endometrial cancer is laparoscopic hysterectomy with bilateral adnexectomy and pelvic and para-aortic lymphadenectomy or sentinel lymph node evaluation, which, in specialized centers, has replaced lymphadenectomy. In cases where the laparoscopic approach is not feasible, a laparotomy is performed (11).

Most cervical cancers are diagnosed at an early stage and are amenable to surgical management (15).

Abdominal radical hysterectomy, along with the standard surgical management approach for early-stage cervical cancer, achieves excellent survival outcomes. As an alternative minimally invasive surgery to abdominal radical hysterectomy, laparoscopic radical hysterectomy has been used since the early 1990s (16).

The better perioperative outcomes of laparoscopic than abdominal radical hysterectomy are well accepted, despite a lack of well-designed prospective randomized controlled trials. Compared with abdominal radical hysterectomy, laparoscopic one is associated with less estimated blood loss, reduced transfusion requirement, a shorter hospital stay, and less postoperative complications (17).

The gynecologic surgery scenario changed substantially in 2005 with the approval of the use of robotic surgery. Since then, robotic radical hysterectomy and robotic radical trachelectomy have increasingly been used in the surgical treatment of early-stage cervical cancer (18).

In the last 10 years, the offer of minimally invasive therapies, and in particular robotic surgery, has increased in the treatment of uterine cancer, to the detriment of laparotomic surgery (19).

Compared with conventional laparoscopic surgery, robotic surgery platforms have several advantages, including

improved instrument dexterity, higher degrees of freedom for instrument movement, a three-dimensional view with a higher magnification, and filtered tremor (20).

Even as far as outcomes are concerned, robotic surgery applied to uterine cancer seems to be better than laparoscopic in terms of hospital stay, return to normal activity, return to a normal diet, conversions to laparotomy, operative complications, blood loss, and overall complications (21).

It is therefore understandable that the resonance of this approach is rapidly increasing, not least because of the short learning curve related to the technology use (22, 23).

Robotic surgery is, on the contrary, characterized by high initial purchase costs of the technology and additional maintenance and surgical costs, the latter higher than those of the laparoscopic technique (12, 19).

In particular, the greatest proportion of robotic hysterectomy costs seems to be associated with time spent in the operating room (24).

Based on the available scientific evidence, we can therefore state that robotic surgery has a strong potential for improving outcomes for patients with malignant neoplasms of the uterus, but at high costs when compared with laparoscopic and laparotomic approaches. The objectives of our study are (a) to assess the value of surgical admissions for malignant uterine cancer in a University Hospital through an analysis of their costs, revenues and outcomes by comparing laparotomy, laparoscopic, and robotic surgery and (b) to assess the economic sustainability of robotic procedures in the same context.

Materials and methods

This study is compliant with the Local Ethical Committee Standards of the Fondazione Policlinico Universitario Agostino Gemelli (FPG) Scientific Research and Care Institute (IRCCS). It was carried out in accordance with the Helsinki Declaration and EU Regulation 2016/679 (GDPR).

A search was conducted by accessing the FPG repository for aggregated and anonymized data, and hospitalizations between 1 January 2019 and 31 October 2021 for malignant uterine cancer surgery were selected according to the National Outcomes Program criteria (25). Among them, those whose discharge hospital form (SDO) reported the ICD9CM codes of at least one surgical procedure on uterus and uterine adnexa and lymph nodes were included in the analysis. Hospitalizations in which the operating session included urinary procedures in addition to uterine surgery were excluded from the analysis, since urinary procedures give rise to different hospitalization trajectories than gynecological surgery alone, both in terms of hospital stays and DRG classification, without taking into account the greater oncological severity of a gynecological tumor that has attacked the urinary tract. Based on ICD9CM codes, the included hospitalizations were subsequently stratified, according to the surgical approach, in laparotomy, laparoscopic, and robotic interventions. For each surgical approach, mean values (with 95% confidence intervals, CIs) were calculated for the following variables: DRG (diagnosis-related group) amount; costs of ordinary inpatient stay, intensive care unit inpatient stay, operating rooms, medical devices, and other healthcare services; and hospitalization's economic margin (i.e., the difference between revenues and costs incurred by the hospital). In the case of robotic surgery, the cost of using the devices took into account the running costs of the robot for the hospital. The ANOVA test was used to assess whether mean values in the three scenarios (laparotomic, laparoscopic, and robotic) were different. In case of statistically significant differences between the three groups detected by the ANOVA test, we proceeded with two-by-two comparisons, to assess differences in means values with the Student's t-test: p-values ≤ 0.05 were considered statistically significant. Moreover, for each surgical approach, the percentage of readmissions within 30 days (95% CI) from hospital discharge was considered. Differences in 30-day readmissions frequency were assessed through relative risks (RRs) of 30-day readmission, calculated for the three surgical approaches compared to each other (laparoscopic vs. robotic, laparotomy vs. robotic, and laparotomy vs. laparoscopic surgery).

Finally, considering the average costs and revenues of robotic and laparoscopic procedures, a break-even analysis was carried out. The break-even analysis aims to establish a threshold within which costs and revenues for a given output will balance (26). In our case, we evaluated surgical production according to two basic modalities: classic laparoscopy and robot-assisted laparoscopy. These two approaches to the same surgical procedure (and thus to achieve the same output (DRG), for which the hospital receives the same revenue) are expected to have different production costs, especially considering the operating costs of the robot. The economic margin of robotic procedures was then evaluated against the margin of non-robotic procedures to establish sustainability scenarios for the hospital. From the point of view of hospital management, interested in pursuing value and sustainability in healthcare, it evaluated the volume of robotic and non-robotic surgical admissions for which costs and revenues (sum of DRGs) for hospital are equivalent, according to the logic of supply governance.

Thus, the formula used in the break-even analysis was the following equation: Number of robotic procedures × (Revenues of robotic procedure admissions − costs of robotic procedure admissions) − Number of laparoscopic procedures × (Revenues of laparoscopic procedure admissions − costs of laparoscopic procedure admissions) = 0.

Normalizing the number of laparoscopic procedures to the value 1 and considering the margin as the difference between revenues and costs, it is possible to make the equation

explicit in these terms: Number of robotic procedures = –(Margin of laparoscopic procedure admissions)/(Margin of robotic procedure admissions). The analysis was conducted on the central mean values and extreme values of the confidence intervals.

Statistical analysis was performed by using STATA software (version 17).

Results

A total number of 1336 hospitalizations were included in the study, 366 with robotic, 591 with laparoscopic, and 379 with laparotomy surgery. Tables 1, 2, respectively, report descriptive statistics for hospitalizations considered and differences among the three hospitalizations' categories based on the comparison of the three surgical approaches to each other. Hospitalizations with laparotomy surgery had the highest average DRG reimbursement rate (6269.19 €; 95%CI: 6237.26 €−6301.11 €), length of stay (6.24; 95%CI: 5.96–6.53), and length of stay costs (1997.68 €; 95%CI: 1907.14–2088.22 € and 91.82 €; 95%CI: 46.68 €−136.96 € for ordinary inpatient stay and ICU inpatient stay, respectively), other health service costs (331.13 €; 95%CI: 304.02 €−358.24 €), operating rooms costs (2843.35 €; 95%CI: 2769.34 €−2917.36 €), and 30-day readmissions percentage (4%; 95%CI: 2.0%−5.9%).

Hospitalizations with robotic surgery had the lowest DRG average reimbursement rate (6038.63 €; 95%CI: 5972.11 €−6105.16 €), length of stay (3.36; 95%CI: 3.14–3.58), average length of stay costs (1074.54 €; 95CI: 1003.78 €−1145.29 € and 72.13 €; 95%CI: 38.89 €−105.37 € for ordinary inpatient stay and ICU inpatient stay, respectively), and 30-day readmissions percentage (1.4%; 95%CI: 0.2%−2.6%) and the highest medical devices average costs (3549.37 €; 95%CI: 3459.32 €−3639.43 €).

Hospitalizations with laparoscopic surgery had the lowest other health service costs (184.65 €; 95%CI: 172.76 €−196.54 €), operating rooms costs (2044.07 €; 95%CI: 1992.34 €−2095.81 €), and medical device costs (660.02 €; 95% CI: 622.53 €−697.52 €) (Table 1).

ANOVA shows significant differences ($p < 0.001$, Table 1) among the averages values of the three approaches (laparotomic, laparoscopic, and robotic), with the exception of the costs of intensive care, which, however, in fact concern a minority of hospitalizations.

Robotic surgery, compared to laparotomy, was characterized by significantly lower DRG reimbursement ($p < 0.001$), length of stay ($p < 0.001$), and 30-day readmissions percentage ($p = 0.029$) and significantly higher medical device costs ($p < 0.001$). All other cost items were significantly lower ($p < 0.001$), except for ICU inpatient stay cost ($p = 0.494$) (Table 2).

Laparoscopic surgery, compared to laparotomy, showed significantly lower DRG reimbursement ($p < 0.001$) and length

TABLE 1 Costs and revenues of hospitalizations for malignant uterine cancer surgery: ANOVA.

	Robotic surgery (n. 366 hospitalizations)		Laparoscopic surgery (n. 591 hospitalizations)		Laparotomy surgery (n. 379 hospitalizations)		ANOVA
	Mean	CI 95%	Mean	CI 95%	Mean	CI 95%	*p*
DRG reimbursement rate	6,038.63 €	5,972.11 € 6 105.16 €	6,054.07 €	6, 000.06 € 6,108.09 €	6,269.19 €	6,237.26 € 6,301.11 €	<0.001
Lenght of stay	3.36	3.14 3.58	3.55	3.41 3.70	6.24	5.96 6.53	<0.001
Ordinary inpatient stay cost	1,074.54 €	1,003.78 € 1,145.29 €	1,136.51 €	1,090.09 € 1,182.94 €	1,997.68 €	1,907.14 € 2,088.22 €	<0.001
ICU inpatient stay cost	72.13 €	38.89 € 105.37 €	46.70 €	22.77 € 70.63 €	91.82 €	46.68 136.96	0.143
Other health services cost	219.33 €	202.41 € 236.25 €	184.65 €	172.76 € 196.54 €	331.13 €	304.02 € 358.24 €	<0.001
Operating rooms cost	2,078.51 €	2,023.41 € 2,133.61 €	2,044.07 €	1,992.34 € 2,095.81 €	2,843.35 €	2,769.34 € 2,917.36 €	<0.001
Medical devices cost	3,549.37 €	3,459.32 € 3,639.43 €	660.02 €	622.53 € 697.52 €	699.44 €	657.47 € 741.40 €	<0.001
Economic margin	−1,069.18 €	−1,240.44 € −897.92 €	1,692.21 €	1,531.75 € 1,852.66 €	188.28 €	−10.99 € 387.55 €	<0.001
30-days readmissions	1.4%	0.2% 2.6%	2.0%	0.9% 3.2%	4.0%	2.0% 5.9%	-

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TABLE 2 Differences among the three hospitalizations' categories based on the comparison of the three surgical approaches to each other (Student's *t*-test).

	Differences between robotic and laparoscopic surgery				Differences between robotic and laparotomy surgery				Differences between laparoscopic and laparotomy surgery			
	Mean	CI 95%		*p*	Mean	CI 95%		*p*	Mean	CI 95%		*p*
DRG reimbursement rate	−15.44 €	−101.87 €	71.00 €	*0.726*	−230.55 €	−303.67 €	−157.43 €	***<0.001***	−215.11 €	−287.34 €	−142.88 €	***<0.001***
Lenght of stay	−0.19	−0.45	0.06	*0.135*	−2.88	−3.25	−2.52	***<0.001***	−2.69	−3.01	−2.37	***<0.001***
Ordinary inpatient stay cost	−61.98 €	−143.19 €	19.24 €	*0.135*	−923.14 €	−1 038.76 €	−807.53 €	***<0.001***	−861.16 €	−963.13 €	−759.20 €	***<0.001***
ICU inpatient stay cost	25.43 €	−14.73 €	65.59 €	*0.214*	−19.69 €	−76.15 €	36.77 €	*0.494*	−45.12 €	−96.32 €	6.08 €	*0.060*
Other health services cost	34.68 €	14.52 €	54.84 €	***<0.001***	−111.80 €	−144.06 €	−79.54 €	***<0.001***	−146.48 €	−176.15 €	−116.81 €	***<0.001***
Operating rooms cost	34.44 €	−44.42 €	113.29 €	*0.392*	−764.84 €	−857.75 €	−671.93 €	***<0.001***	−799.28 €	−889.73 €	−708.83 €	***<0.001***
Medical devices cost	2 889.35 €	2 803.79 €	2 974.89 €	***<0.001***	2 849.94 €	2 750.35 €	2 949.53 €	***<0.001***	−39.41 €	−97.09 €	18.27 €	*0.180*
Economic margin	−2 761.38 €	−3 006.11 €	−2 516.66 €	***<0.001***	−1 257.46 €	−1 521.41 €	−993.53 €	***<0.001***	1 503.93 €	1 247.46 €	1 760.39 €	***<0.001***
30-days readmissions	−0.7%	−2.3%	1.0%	*0.450*	−2.6%	−4.9%	−0.3%	***0.029***	−1.9%	−4.2%	0.3%	*0.075*

The italics and bold values indicated the calculated p-values of the statistic that are statistically significant ($p \leq 0.05$).

TABLE 3 Relative risk of 30–day readmission of the three surgical approaches compared to each other.

	RR	IC 95%	
Laparoscopic vs. robotic surgery	1.49	0.53	4.18
Laparotomy vs. robotic surgery	2.90	1.06	7.89
Laparotomy vs. laparoscopic surgery	1.95	0.92	4.12

of stay ($p < 0.001$), but no statistically significant difference for 30-day readmissions percentage ($p = 0.075$). All cost items were significantly lower, except for ICU inpatient stay ($p = 0.06$) and medical devices ($p = 0.18$) (Table 2).

Robotic surgery, compared to laparoscopic surgery, was characterized by a lower DRG remuneration, hospital length of stay, and 30-day readmissions percentage, although without statistically significant differences ($p = 0.726$, $p = 0.135$, and $p = 0.45$, respectively), and significantly higher device costs and other health service costs ($p < 0.001$) (Table 2).

Average economic margins were−1069.18 € (95%CI: −1240.44-−897.92 €) for robotic, 1692.21 € (95%CI: 1531.75 €−1852.66 €) for laparoscopic, and 188.28 € (95%CI: −10.99 €−387.55 €) for laparotomy surgery (Table 1). Differences in economic margins of the three approaches compared with each other (robotic vs. laparotomy, laparoscopic vs. laparotomy, and robotic vs. laparoscopic surgery) were all statistically significant ($p < 0.001$) (Table 2).

RRs of 30-day readmission were 1.49 (95%CI: 0.53–4.18), 2.90 (95%CI: 1.06–7.89), and 1.95 (95%CI: 0.92–4.12) for laparoscopic vs. robotic, laparotomy vs. robotic, and laparotomy vs. laparoscopic surgery, respectively. Laparotomy's 30-day readmission RR was almost three times that of robotic surgery, albeit with a confidence interval bordering on statistical significance (Table 3).

Regarding the break-even analysis, the comparison of the economic margin (understood as the difference between costs and revenues) of laparoscopic surgery with that of robotic surgery showed that on average, for each malignant uterine cancer elective surgery performed laparoscopically, 1.58 elective robotic surgeries are sustainable for the hospital (95% CI: 1.23–2.06). In fact, admissions with laparoscopic procedures have an average positive margin of about 1690 euros, while admissions with robotic procedures generate a loss of about 1070 euros: It follows that one admission with a laparoscopic procedure theoretically provides the capacity to grant about 1.5 admissions with robotic procedures.

Discussion

Our results highlight an improvement in terms of patient outcomes, expressed by the 30-day readmissions indicator, when using the robotic surgical technique, compared to both

laparoscopic and laparotomic ones. Nevertheless, statistical significance is obtained only when the robotic surgery is compared with laparotomy; statistical significance on the relative risk of readmission is not obtained comparing laparoscopy with laparotomy.

Data show, in terms of duration of hospitalization as well, that the robotic surgery allows a reduction in the parameter vs. both laparoscopic and laparotomic surgeries, but it is statistically significant only when compared to the latter.

The advantages of robotic surgery in terms of outcome identified by our study are in line with the literature. A systematic review and meta-analysis by Ind et al. (21), comparing the robotic and laparoscopic techniques, reported that duration of hospitalization was lower in patients treated with robotic surgery. Other outcomes considered by Ind et al. were blood loss, number of conversions to laparotomy, and overall complications, all of which were lower in patients treated with the robotic technique (21).

Similarly, the retrospective study by Casarin et al. (19), analyzing data from hospitals in the United States between 2008 and 2015 inherent to hysterectomies in adult patients, supported the finding that the robotic surgery results in a shorter hospitalization when compared to the laparoscopic and laparotomic techniques. Moreover, the study showed a lower 30-day complications rate for robotic surgery compared with laparotomy. In terms of 30-day readmissions, it reported data confirming our observations, with a lower rate for robotic surgery compared to laparotomy (19).

Regarding the evaluation of costs, our analysis shows that robotic surgery admission has lower costs than laparotomic technique in several parameters, assuming statistical significance in case of costs related to the ordinary inpatient stay, other health services, and operating room.

On the contrary, the expenses incurred with robotic surgery in terms of medical devices are significantly higher than the costs associated with laparotomic technique. These data result in a negative economic margin of robotic surgery in comparison with laparotomy. In addition, it can be seen that economic revenue for admission with robotic surgery is statistically significantly lower than revenue for admission with laparotomic surgery. This is certainly attributable to the higher complexity of patients for whom open surgery is required, as they are not suitable for robotic or laparoscopic procedures. A higher complexity of patients in fact generates a higher reimbursement for the hospital, in accordance with the logic of DRG reimbursement (27) (in our sample, it was found that laparotomy surgery is more often associated with a diagnosis of ovarian malignancy, generating a DRG with a higher economic amount).

Compared to the laparoscopic technique, however, the robotic technique has a reduced ordinary inpatient stay cost, although not statistically significant, which presents higher costs related to ICU inpatient stay, operating room, other health services, and medical devices, with statistical significance achieved for the last two only. The difference in the economic value of medical devices, considering the use of the robot and its management costs, is huge, representing almost the whole difference in the economic margin, especially in light of the fact that the value of the DRG amount is not significantly different in the comparison between robotics and laparoscopic surgery. It can be seen that the average difference in the value of medical devices in the two approaches is around € 2,890; the average difference in the value of the operating margin is about € 2,760, showing how all the economic loss in the comparison between robotic and laparoscopic surgery is precisely attributable to the management costs of the technologies used in the operating room. In view of this, it is also useful to underline that the DRG rates in force in Italy do not provide for specific reimbursements related to surgical approaches, except in some cases (e.g., laparoscopic cholecystectomy) (27), reimbursing hospitalizations according to a classification which almost always disregards the technology used.

The DRG system derives from the research on the hospital production function started in 1967 by the group of Yale University, in the United States, coordinated by Robert Fetter (28, 29).

The DRG classification system is a method of categorizing patients for health insurance purposes, to control costs and facilitate reimbursement by third-party providers for the use of medical services and equipment. Using the DRG system, patients are classified, according to a number of variables, into a limited number of groups to form clinically meaningful, but relatively homogeneous, patterns of resource consumption (30).

In Italy, an initial version of the Medicare DRGs was used from the 1st of January 1995 to the end of 2005. A subsequent version of the Medicare DRGs was used from the beginning of 2006 to the end of 2008. The current version of the Medicare DRGs, finally, has been in use since the beginning of 2009; therefore, in our country, there is a delay in updating the DRGs (31). The process of obsolescence toward which DRG are heading partly justifies the economically disadvantageous margins that robotic surgery suffers in terms of reimbursement. This is an example of healthcare payment systems failing to keep pace with the technological advances in modern medicine (32).

Concerning our findings, although at a first analysis of our data the robotic technique does not seem to ensure concrete economic advantages when compared to the other two techniques, it is necessary to consider the relatively recent introduction of robotic surgery in our University Hospital.

Our study shows that even now, the costs of the operating room with robotic surgery, one of the items with greater economic weight, are significantly lower than the laparotomic technique and slightly lower than the laparoscopic technique: We expect that, as a consequence of the learning curve, an improvement in terms of skill by our surgeons will lead to

a reduction in operating time and a consequent reduction in operating room costs.

Exemplary in this regard is the work of Avonstondt et al. in 2017, in which differences between the costs of the robotic technique on its introduction and 5 years later were measured: The results were unequivocal, with a reduction in mean total costs and mean operative costs. The reduction in mean operative costs was given principally by the reduction of anesthesia and mean operating room costs. At once, they reported a reduction in mean procedure time and mean operative time, showing that the decrease in costs was mainly due to reduced operative times (24).

In addition to considerations about the effectiveness of robotic surgery, it is also necessary to take into account the value this technique assumes within a valuable context such as the University Hospital analyzed by our study (33, 34).

This is from the point of view of both the unique gynecological oncology's activity volumes of the hospital in the Italian panorama and the relevant academic value inherent in the practice of robotic surgery (25, 35).

Based on these considerations, and in light of the findings of our study, we can say that, on the one hand, it is certainly neither feasible nor appropriate to preclude the use of robotic surgery in the context examined, but, on the other, it is necessary to search for an effective clinical governance tool to distribute surgical volumes between laparotomic, laparoscopic, and robotic procedures, to ensure the sustainability of malignant uterine cancer surgery in a value-based perspective.

The methodology we used to address this issue is the break-even analysis. It consists of the study of the interrelationships between costs, sales volume, and prices of a business/service/product with the objective of identifying the break-even point. The last is often the time at which the fixed and variable costs involved in the production and distribution of a product are matched by its overall sales; generally, that is the point at which total costs are exactly equal to revenues (26).

The results of the analysis show how, by comparing the economic margin, the break-even point, and consequently the suggested ratio between robotic and laparoscopic surgery, is reached in the value of 1.58. Therefore, about up to 1.5 robotic procedures could be performed for every laparoscopic procedure (three robotic for every two laparoscopic procedures), to make robotic surgery sustainable, safeguarding the economic equilibrium alongside the improvement of health outcomes in the logic of value.

The use of the break-even approach allows to promote the value-based view by identifying a useful criterion for the planning of interventions for uterine malignancies, all of this while ensuring the use of robotic surgery, with its advantages both in terms of surgeon learning curve and clinical outcomes, and the sustainability of the system. However, it is worth pointing out that, as in any break-even analysis, the "zero point" or break-even point depends strictly on how accurately it could be the calculation of revenues and costs, both fixed and variable, for the hospital. In our case, while for revenues we can easily refer to DRG payment system and for variable costs to production factors such as inpatient stays, devices, and operating room occupancy, specific to selected admissions, fixed costs are not immediately reversible on same admissions, for which DRGs have theoretically to pay both fixed and variable costs. In this perspective, one limitation of our break-even analysis is that it essentially concerns living costs per performance output. Our study is not free from some limitations indeed, among which first of all the fact that it is not a multicenter study, an aspect mitigated by the large activity volumes of our hospital in terms of malignant uterine cancer surgery (25). Second, the only outcome indicator used is that of readmissions within 30 days from hospital discharge, data borrowed from administrative sources.

Among strengths, as previously mentioned, there is the large number of cases treated in our hospital which is a reference center at the national level for oncological surgery of the uterus, and the accurate methodology was adopted.

Our study opens up a number of future implications both in terms of healthcare management and research. As for healthcare management, it made it possible to identify, in the context considered, the break-even analysis as a useful tool to support the planning and governance of malignant uterine cancer surgery activities. The systematic application of this tool will allow defining over time the right distribution of robotic, laparoscopic, and laparotomy surgeries' volumes to perform to ensure both quality and economic-financial balance and therefore value of uterine oncological surgery in our University Hospital. Concerning research, this study paves the way for a multicentric study, the extension of outcomes of malignant uterine surgery to be considered and assessed, and the future inclusion of other therapeutic interventions in the analysis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

MS, GA, and AD: conception and design of the study, acquisition, analysis, interpretation of data, drafting the article, and revising the article critically for intellectual content. EL and TO: analysis and interpretation of data and drafting the article. PL: analysis and interpretation of data and revising the article critically for intellectual content. GS and RDAB: conception of the study and

critical revision of the article for intellectual content. All authors contributed to the article and approved the submitted version.

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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.

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Cervical cancer elimination in Italy: Current scenario and future endeavors for a value based prevention

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Background: Cervical Cancer (CC) is a vaccine-preventable disease, and it is treatable if diagnosed early and managed properly. However, it is the fourth most common cancer in women worldwide with about 604,127 cases and 341,831 deaths in 2020. In Italy, it represents the fifth most common cancer in women under 50 years of age with about 2,400 new cases in 2020. The CC elimination is today a global public health goal published by the World Health Organization (WHO) in 2020 and a commitment of the European Union that has included it in Europe's Beating Cancer Plan. Therefore, urgent action is needed, at international and national level, to implement value-based interventions regarding vaccination, screening and timely management of the disease. Our study aims to describe the state of the art of Human Papilloma Virus (HPV) prevention in Italy and to get a consensus on indicators for monitoring the progress toward CC elimination at national level.

Methods: The study envisaged the following activities: research and synthesis of the evidence on strategies and actions for CC elimination at regional Italian level; identification of indicators to monitor such strategies/actions; organization of a multi-stakeholder consensus to reach the agreement on main indicators to be used in Italy.

Results: As for HPV vaccination coverage, the last Italian available data (December 31st, 2020) showed that it was way below the target (95%) with full cycle vaccination coverage ranging from 6 to 61.7% in female adolescents and from 5.4 to 55.4% in male adolescents (2008 birth cohorts). The coverage rate of CC screening is variable with a range of 61.7–89.6%. Furthermore, coverage rates due to organized screening programs (excluding out-of-pocket screening) shows a range from 20.7 to 71.8%. The mapping of the Italian Regions highlighted an important regional heterogeneity in respect to organizational/operational issue of HPV vaccination and CC

screening. Indicators for monitoring CC elimination strategies have been drawn from the Australian experience and distinguished by disease outcomes, vaccination coverage, screening participation and treatment uptake. The highest consensus was reached for the following indicators: CC incidence; detection of high-grade cervical disease; CC mortality; full cycle vaccination coverage; screening participation; high-grade cervical disease treatment rates; CC treatment rates.

Conclusions: The assessment of the current status of CC elimination as overarching goal beyond the achievement of vaccine, screening and treatment targets represents the first step for the identification of interventions to be implemented to accelerate the path toward CC elimination. Based on this and following the WHO call, a value-based approach is proposed to untangle the full benefit of HPV-related cancers elimination strategies and identify priority and best practices.

KEYWORDS

cervical cancer, value-based prevention, vaccination, screening, indicators

Introduction

Human Papilloma Virus (HPV) has been recognized as a carcinogenic agent since 1995 (1). Cervical cancer (CC) accounts for around 80% of all HPV-related cancers (2) and HPV types 16 and 18 are responsible for 72% of all HPV-related cancers whereas HPV31, 33, 45, 52, and 58 account for an extra 17% (3). These HPV types are categorized as oncogenic high-risk (HR) (4).

More than 95% of CC is due to the HPV (5). Most sexually active women and men are infected in their lifetime, and some may be repetitively infected. More than 90% of the infected cases resolve spontaneously, with viral clearance, within two years; however, the persistence of HR-HPV infection can lead to dysplasia and an increased risk of developing cancer (6).

About 604,127 new CC cases are diagnosed annually worldwide with about 342,000 deaths each year (estimations for 2020); this cancer represents the 4th leading cause of woman cancer and the 2nd most common cancer in women aged 15–44 years in the world (4). Furthermore, CC represents the 9th most frequent cancer among European women with more than 58,000 new cases and almost 26,000 deaths each year (4). Epidemiological data vary deeply across Europe also because of differences in prevention policies (7). In Italy, the age standardized incidence rate of CC is 6.9 per 100,000 women (4) with 2,400 new cases in 2020 (8).

CC is a preventable disease, through HPV vaccination and screening, and it is treatable if diagnosed early and managed properly (5). However, the burden of CC is still relevant worldwide. In this light, a Global strategy toward eliminating CC as a public health problem, has been adopted by the World Health Assembly in 2020 (9). This strategy includes a comprehensive approach to CC prevention and control, and proposes lifelong actions through primary, secondary and tertiary prevention interventions. In particular, the strategy of World Health Organization (WHO) proposes a threshold of 4 per 100,000 women-years for CC elimination, and the 90-70-90 actions targets to be met by 2030, namely 90% of girls fully vaccinated with HPV vaccine by age 15 years, 70% of women screened with a high-performance test by 35 years of age and again by 45 years of age, and 90% of women with a CC receiving treatment (90% of women with pre-cancer treated, and 90% of women with invasive cancer managed) (9). Furthermore, according to the WHO, CC prevention should involve a multidisciplinary approach, including community education, social mobilization, vaccination, screening, treatment and palliative care (5, 9).

Following the WHO call, in February 2021, the European Commission (EC) published the Europe's Beating Cancer Plan with the aim of promoting a common fight against the cancer in all European Union (EU) Member States. One of the proposed initiatives concerns precisely the elimination of CC and other HPV-related cancers through the achievement of the 90-90-90 targets by 2030 (10).

In Italy, the current National Immunization Plan (NIP) 2017–2019 provides free HPV vaccination in girls and boys aged 12 years of age and sets a 95% target vaccination coverage (11). Additionally, the NIP recommends HPV vaccination for Men who have Sex with Men (MSM) and women 25 years old, also using the opportunity of the call to the first screening for cervical cancer. The NIP also recommends vaccination according to the guidelines of the Regions (co-payment scheme) for all women (11). Instead, as regards CC screening, the National Prevention Plan 2014–2018 (12) provided that all Italian regions by 2018

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passed from the Pap test to HPV-DNA as the primary test for women aged 30–35. In the National Plan 2020–2025 (13) it is planned to continue in completion of this transition in all regions.

In a current context characterized by increasing economic pressure, health systems worldwide face challenges related to the need to ensure access to high quality healthcare for all citizens. Therefore, evidence-based tools to support a value-based decision-making process are needed also in the prevention field (14, 15). Understanding of the value should be shared by all health actors and be geared toward the goal of maximizing social wellbeing (16). In fact, we are moving from the concept of a value-based health care to the concept of a value-based health system as it is the whole health system that contributes to societal wellbeing (16), thanks also to health promotion and prevention interventions. However, this cannot disregard a deep knowledge of the current scenario. From this perspective, considering the autonomy granted to Italian regions in respect to the development of health strategies, this work was aimed at mapping vaccination and screening policies and strategies in the 20 Italian regions and identifying, through the consultation of a board of Italian experts, the indicators for monitoring the progress toward CC elimination at national level.

Materials and methods

A two-pronged method was used to conduct the study. First, a search of documents and data on HPV vaccination and CC screening policies and strategies in the 20 Italian regions was conducted from June 2021 to March 2022. For this purpose, institutional websites—such as those of the Ministry of Health (www.salute.gov.it), of the National Institute of Health (www.epicentro.iss.it) and of the National screening observatory (www.osservatorionazionalescreening.it) -, regional websites, and the website of the Italian Group for Cervical Cancer Screening (GISCi) (www.gisci.it), were queried using the following search terms: HPV elimination strategies, HPV vaccination uptake and cervical screening. The mapping process was performed by six researchers independently. Then, the items reported in Table 1 were collected in an excel-sheet for each Italian region.

The latest data available on HPV vaccination and screening coverage in Italy refer to the year 2020 while the latest Italian data on cervical screening extension and adherence are those of 2018.

Each Italian region excel-sheet was subjected to the double check of two researchers and then double-checked further by two senior researchers.

Second, a multidisciplinary and multi-stakeholder board of experts has been established to evaluate and validate collected information and data and to achieve a consensus over indicators to monitor the progress toward CC elimination at national level.

TABLE 1 Items on HPV vaccination and cervical screening collected in the mapping process of our study, for each Italian region.

Items on HPV vaccination	Items on cervical screening
Full cycle vaccination coverage in adolescents (females and males)	Cervical screening coverage (total coverage and organized screening coverage)
Vaccination reimbursement policies (free of charge/co-payment) for different targets such as: - adolescents, - people with HIV infections, - Men who have Sex with Men (MSM), - people with previous diagnosis of HPV-related lesions.	Screening extension and adherence with different HPV detection methods (HPV-DNA test/Pap smear testing)
	Target age for screening with HPV-DNA test
	Presence/absence of a specific strategy for women previously vaccinated for HPV
Presence/absence of a regional coordination on vaccination	Presence/absence of a regional coordination on screening
	Presence/absence of a regional diagnostic-therapeutic-care pathway (DTCP) for CC management.

The board was made up of 17 experts selected among health care professionals with relevant knowledge and experience in HPV-related diseases prevention and management: four members of the Italian scientific society of hygiene, preventive medicine and public health experts in the vaccination field; two members of GISCi experts in cancer screening; two gynecologists, an oncologist, a referent of the Italian cancer registry, an andrologist, a radiotherapist, three pediatricians (two from the hospital setting and one from the territorial setting), an otolaryngologist and a general practitioner, all referents of their respective scientific societies.

The board was involved in two virtual meetings and was requested to answer an online survey launched through Google Platform in between the two meetings. In the first virtual meeting, in December 2021, the research working group shared collected information and data and introduced the indicators to monitor CC elimination in Italy. Regarding indicators, the Australian report on progress toward the elimination of CC was considered (17). Australia is a world leader in CC prevention and control, having achieved a halving of incidence and mortality through the cytology-based National Cervical Screening Program first implemented in 1991; and the world's first national HPV vaccination program in 2007, which resulted in a significant reduction in rates of HPV infection and precancerous cervical lesions. With the transition from cytology to HPV based screening in December 2017 and the introduction of the nonavalent HPV vaccine in 2018, Australia is expected to be the first country to reach the WHO definition of eliminating CC as a public health problem by 2030. Australia is also a world leader in research and

surveillance documenting the impact of CC control programs. In fact, since 2018, Australian public health and clinical researchers have been collaborating in the Center of Research Excellence in Cervical Cancer Control. Additionally, Australia was the first country to produce a comprehensive report on Australia's progress toward CC elimination, proposing 11 key indicators to monitor progress toward the achievement of WHO objectives (17).

For these reasons, the 11 Australian indicators grouped into four components (disease outcomes, vaccine coverage, screening participation, treatment) were proposed to the group of Italian experts in order to evaluate their applicability and usefulness in Italy.

The online survey was aimed at collecting experts' positions in respect to the utility of the 11 indicators (binary response: yes/no). The survey was live for four weeks to allow all experts to take part and a reminder was sent one week prior to the deadline to ensure maximum participation.

In the second virtual meeting, results of the survey were shared and a final agreement was reached though a plenary discussion led by three experts, scientific managers of the project (two experts in public health and a gynecologist).

These activities were completed on March 9, 2022.

Results

The main results of our study are reported in the following sections: HPV vaccination in Italian regions, screening for CC in Italian regions, and results from the experts' consultation.

The results of the mapping of policies and strategies in Italian regions are summarized in Tables 2, 3.

HPV vaccination in Italian regions

Despite the efforts to reach the goal of 95%, the last Italian available data (December 31st, 2020) showed that vaccination coverage was way below the target with full cycle vaccination coverage ranging from 6 to 61.7% in female adolescents (2008 birth cohort), and from 5.4 to 55.4% in male adolescents (2008 birth cohort). Table 2 shows an important variability among the Italian regions and the two autonomous provinces (A.P.) both for vaccination coverage and for HPV vaccination policies and strategies. For example, as of March 2022 Piemonte and Lombardia regions provide girls who were included in the target population with lifetime free of charge access to vaccination. Free of charge vaccination is also offered to people belonging to at-risk groups, as follows: people with diagnosis of HIV infection in eight regions and in two A.P. (47.6%) and MSM in 9 regions and in two A.P. (52.4%). Regarding people with HPV-related lesions, 16 regions and two A.P. (85.7%) offer free of charge vaccination to women and three out of them also offer it to men. However, it should be noted that from March to today the offer free of charge vaccination to women with HPV-lesions has also been extended to the other Italian regions. Co-payment with no age limit is provided in 57% of regions (10 regions and 2 A.P), but one of them (Marche) offers this service only to women. The presence of coordination at a regional level is evidenced in seven regions (33.3%).

CC screening in Italian regions

The screening coverage data refer to 2020, except for Lombardy whose available data are updated to 2019. The coverage rate of CC screening is variable (Table 3) with a range of 61.7–89.6%. Furthermore, coverage rates due to organized screening programs (excluding out-of-pocket screening) shows a range from 20.7 to 71.8%.

At the time of our analysis, the transition from the Pap test to HPV-DNA as the primary test for women aged 30-35 proposed by the National Prevention Plan 2020–2025 (13) was still ongoing in one region (Puglia). Furthermore, data for the calculation of the indicators of screening extension and adherence refer to 2018, when the programs with HPV-DNA were in progress in all regions except four (Friuli Venezia Giulia, Marche, Puglia and Sardinia). Indicators were calculated for both HPV-DNA test and Pap smear. As regards HPV-DNA test the extension ranges from 0 in the Friuli Venezia Giulia, Marche, Puglia and Sardinia regions to 100% in the Emilia-Romagna, AP of Trento, Piemonte and Veneto; the adherence ranges from 19.8% in Sicily to 87.6% in Campania. As regards Pap smear test, the extension ranges from 8.3% in the Umbria region to 94.8% in the AP of Bolzano; the adherence ranges from 5.1 in the Molise region to 90.3% in the Abruzzo region.

As of January 2022, target populations for HPV-DNA test differ across the regions. In 13 (65%) regions, HPV-DNA testing is offered to women older than 30 years of age, whereas in seven (35%) the target population is represented by women older than 35 years of age. Recently, the Puglia region disclosed that it will perform the HPV-DNA test starting from the age of 25 (start of the program from September 2022).

At the time of data analysis, the presence of a regional coordination for the screening is evidenced in all regions and A.P. except for Campania region.

The presence of a regional DTCP specific for CC management was available in eight regions (38.1%).

Eventually, regarding the rescheduling of the screening for women vaccinated with a complete cycle, within the National Prevention Plan 2020–2025 (13) is given explicit mandate to the Regions to draw up a specific evidence-based strategy, and, currently, the first Region that has implemented this recommendation is Veneto.

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TABLE 2 Summary of information and data on HPV vaccination policies and strategies in the Italian regions.

	Abruzzo	Basilicata	Calabria	Campania	Emilia Romagna	Friuli Venezia Giulia	Lazio	Liguria	Lombardia	Marche	Molise	Trentino Alto Adige-AP Bolzano	Trentino-Alto Adige-AP Trento	Piemonte	Puglia	Sardegna	Sicilia	Toscana	Umbria	Valle d'Aosta	Veneto
HPV—Vaccination																					
Vaccination coverage—girls (2008 cohort) (%)	29.8	43.6	40.9	24.8	51.1	9	19.1	46.2	17.8	29	34.8	13.9	61.7	49	44.8	15	22.6	53.4	53.9	6	17.9
Vaccination coverage—boys (2008 cohort) (%)	18.5	38.2	31.2	12.8	46.9	8	9.6	37	16.6	22.5	29.5	10.4	55.4	43.5	39.1	12.3	14.9	40.5	46.9	5.4	16.4
Free vaccination in the female population without limits of age									X					X							
Free of charge vaccination of people with HIV infections					X	X	X	X	X	X		X	X					X			X
Free of charge vaccination of people at risk and MSM		X				X	X		X		X	X	X	X	X			X			X
Free of charge vaccination of people with previous diagnosis of HPV-related lesions		X M/W		X	X	X	X	X	X	X	X M/W	X	X	X	X	X	X M/W	X	X		X
Co-payment for all other groups	X M/W		X M/W		X M/W	X M/W	X M/W			X W		X M/W	X M/W	X M/W	X M/W				X M/W		X M/W
Regional coordination		X			X			X		X				X				X			X

MSM, Men who have Sex with Men; M/W, for men and women; AP, autonomous provinces.

Results from the experts' consultation

The response rate to the online survey was 100%. The results regarding the agreement on the utility of the 11 indicators drawn from the Australian experience are reported in Table 4. Overall, the majority of experts agreed on the utility of all the indicators. Nonetheless, in respect to diseases outcome, CC incidence and detection of high-grade cervical disease in the screened women have reached unanimous consent. In respect to vaccination, full cycle vaccination coverage was assigned most importance. In respect to screening and treatment, screening participation and treatment rates of high-grade cervical disease and CC reached the highest consensus. Nevertheless, from the plenary discussion it emerged that the monitoring of adherence to screening at 35 and 45 years of age is relevant and possible at national/regional level.

Discussion

This paper reported the status of vaccination and screening policies and strategies in Italy highlighting two main important issues: the first one is that Italy must still work to achieve the targets of the WHO Global Strategy whereas the second one is

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TABLE 3 Summary of information and data on cervical screening policies and strategies in the Italian regions.

	Abruzzo	Basilicata	Calabria	Campania	Emilia Romagna	Friuli Venezia Giulia	Lazio	Liguria	Lombardia	Marche	Molise	Trentino Alto Adige-AP Bolzano	Trentino-Alto Adige-AP Trento	Piemonte	Puglia	Sardegna	Sicilia	Toscana	Umbria	Valle d'Aosta	Veneto
Cervical screening																					
Coverage, 2020 (%)	75.7	73.6	61.7	64.9	89.3	89.5	85.9	86.5	83.4*	84.6	64.9	89.6	85.1	84.5	75.4	73.3	69.5	88.2	87.3	64.9	88.4
Coverage of organized screening, 2020 (%)	45.6	45.6	33.6	20.7	68.5	66.5	39	41.1	31.2*	56.1	27.6	56	57.7	63.7	33.5	58	46.7	71.8	66.5	27.6	60.7
Extension of HPV-DNA test, 2018 (%)	72	70.1	2.1	2.4	100	0	69	9.6	1.7	0	53.4	13.5	100	100	0	0	10.6	81.5	75.6	88.2	100
Adherence to HPV-DNA test, 2018 (%)	56.7	62.7	28.7	87.6	61.1	0	29.3	82.8	46.7	0	78.3	33.6	66.8	43.9	0	0	19.8	53.4	61.9	71.8	63.5
Extension of pap-test, 2018 (%)	9.5	12.7	23.5	55.7	29.6	80.3	55.6	83.9	22.9	86.6	83.9	94.8	38.9	15.6	84.2	80.7	82.6	38.6	8.3	54.4	10.1
Adherence to pap-smear test, 2018 (%)	90.3	59	31.7	23.8	58.2	64.5	27.3	29.8	49.9	42.4	5.1	30.1	53	44.5	33.2	41.8	21.6	51	68.5	64.3	59
Regional coordination	X	X	X	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Target population of HPV-DNA test (years old)	>30	>35	>30	>35	>30	>35	>30	>30	>35	>30	>35	>30	>30	>30	≥25 (from September 2022)	>30	>35	>35	>30	>30	>30
Regional DTCP		X		X	X		X			X					X			X	X		
Specific strategy for previous vaccinated women																					X

DTCP, Diagnostic-therapeutic-care pathway; AP, autonomous provinces; *Data refer to the year 2019.

that Italian regions show an undue variability that might slow down the achievement of the targets.

Considering the actions proposed by the WHO strategy and in particular the goal of vaccinating 90% of girls with HPV vaccine by age 15 years, our data shows that if the provision of vaccination to the target group is satisfied in all Italian regions, coverages are still not optimal. Furthermore, referring to the other NIP indications, namely vaccination in MSM and in women aged 25 years old, only slightly more than half of the regions offer the HPV vaccination to the MSM, and still not all regions actively offer vaccination at the first screening.

However, it is important to point out that some Italian regions have extended the vaccination to other targets at risk, such as, for example, women treated for HPV-related lesions.

On the contrary, with respect to the possibility to access vaccination in co-payment all regions are aligned, with someone even providing for the extension to the male population. In addition, worthy of note is to report that, at the time of our analysis, two Italian regions (Lombardia and Piemonte) reserve

TABLE 4 Evaluation of the Italian experts regarding the 11 indicators to be used to monitor the interventions to be implemented for the CC elimination in Italy.

Indicators	Do you agree with the evaluation of the following indicators to monitor the progress toward cervical cancer in Italy?	Yes *N* (%)	No *N*(%)
Disease outcomes	CC incidence	17 (100%)	0 (0%)
	Detection of high-grade cervical disease	17 (100%)	0 (0%)
	CC mortality	16 (94.1%)	1 (5.9%)
	Prevalence of HPV infection	15 (88.2%)	2 (11.8%)
Vaccine coverage	HPV vaccine initiation by age 15	13 (76.5%)	4 (23.5%)
	HPV vaccine completion by age 15	16 (94.1%)	1 (5.9%)
Screening participation	Screening participation	15 (88.2%)	2 (11.8%)
	Screening participation by age 35 and 45 year	12 (70.6%)	5 (29.4%)
Treatment uptake	Colposcopy attendance	14 (82.4%)	3 (17.6%)
	High-grade cervical disease treatment rates	15 (88.2%)	2 (11.8%)
	Cervical cancer treatment rates	15 (88.2%)	2 (11%)

free of charge vaccination to life for women who have returned to the primary target, a strategy that can facilitate the improvement of vaccination coverage.

Nevertheless, as vaccination coverage in Italy is still very far from the 90% target set by WHO it is necessary to implement targeted actions aimed at implementing health education, as also proposed in the WHO strategy (9). Furthermore, combining education, information, and communication activities with other kinds of interventions could led to more effective and lasting results. In fact, multicomponent strategies are shown to achieve the best results (18).

Indeed, the Italian national health system should work on the integration of different approaches, including personalized reminders, information and educational activities aimed at increasing adolescents', parents' and healthcare professionals' (HCPs) awareness and knowledge about HPV infection and vaccination, training programs for HCPs on communication strategies with parents and adolescents, and facilitated access to vaccination also including vaccination programs in schools (18) as done in Australia since 2007 (17).

Australia, thanks to the primary and secondary prevention strategies implemented (19, 20), is expected to be the first country to reach the WHO definition of eliminating CC as a public health problem by 2030. In fact, in 2011–2015, the annual incidence of CC in Australia was 6.3 cases per 100,000 women (17) and it has been projected to decrease below 4 new cases per 100,000 women by 2030 (17).

In respect to screening, in Italy, the coverage is largely variable across regions and A.P. Furthermore, considering that the objective set by the WHO refers to the HPV-DNA test, it must certainly be highlighted that yet not all the Italian regions have completed the process of implementation of the HPV-DNA test within screening programs. Moreover, also in the regions where the HPV-DNA test is offered, an extension of 100% is not always achieved. It should be also noted that adherence to the screening with HPV-DNA testing is still extremely variable among different Italian regions. It follows that even in respect to screening there is still a lot to work. Surely greater regional coordination action, currently present in almost all regional realities, would allow for a more homogeneous offer.

Despite the effectiveness and cost-effectiveness of prevention interventions, investment in disease prevention remains low in many countries (21). Among the barriers, there are the unwillingness to invest in actions that generally generate positive benefits in the long-term horizon and the difficulty of different actors to immediately enjoy the health benefits obtained from prevention (16). Therefore, in order to remove these barriers and to improve the citizens' health and the health systems value, especially in priority areas for public health such as that of the control of HPV-related cancers, actions should be taken following the concept of value proposed by Expert Panel on Effective Ways of Investing in Health (EXPH) of the EC in 2019. The proposed concept is built on four value-pillars: appropriate care to achieve patients' personal goals (personal value), achievement of best possible outcomes with available resources (technical value), equitable resource distribution across all patient groups (allocative value) and contribution of healthcare to social participation and connectedness (societal value)" (22). This approach is also in line with the perspective of a value-based health system proposed by the WHO and the European Observatory on Health Systems and Policies (16). According to these international institutions, the main objective of health systems is to maximize social wellbeing, understood as the value created by the system as a whole, including health promotion and disease prevention (16). In particular, as stated by the EXPH, the guiding principles are access, equity, quality, performance, efficiency and productivity (optimization and distribution of resources) (22).

According to this value-based perspective, the involvement of all stakeholders—governments, scientists, healthcare professionals, patients and citizens, providers and industries—is the key to implement high-value health care (22). Similarly, an appropriate governance is necessary (16). Greer and colleagues (23) present a five-dimensional framework for designing and assessing governance of health systems, defined TAPIC

(Transparency, Accountability, Participation, Integrity, and Policy capacity). This framework also underlines the need to identify useful indicators to measure health improvements associated with value-based interventions (16).

The lack of nationwide data on the whole HPV-related diseases epidemiology and treatment indicators could undermine the assessment of the quality and the performance of the health system. In fact, a fundamental action for a proper governance of healthcare and health systems as a whole is the identification and the routine use of indicators, as done in Australia for monitoring CC elimination. Our survey with the experts revealed the utility and applicability of the Australian indicators also in Italy, even though some critical issues have been pinpointed in respect to the availability and access to data in particular in respect to disease outcomes and treatment. In this respect, the active and informed involvement of all relevant stakeholders (14) will play a fundamental role in both making the constant evaluation possible and ultimately achieving the goal of eliminating the CC and controlling all other HPV-related diseases.

In September 2022, the document "Roadmap to accelerate the elimination of cervical cancer as a public health problem in the WHO European Region 2022–2030" was also published with the aim to implement the Global strategy to accelerate the elimination of CC as a public health problem in the European Region (24). This document emphasizes that robust surveillance and health information systems are critical for monitoring and evaluating the impact of the proposed roadmap. Furthermore, it is proposed that Member States should develop or update their national action plans, outlining clear strategies and mechanisms to achieve the targets and goals outlined in the regional roadmap; and that Member States should develop costed comprehensive national action plans with priority actions and a monitoring, evaluation and accountability framework, with active engagement from national, regional and global stakeholders. As with Australia, the European roadmap, in line with the global strategy, will need to include metrics to monitor regional progress toward the 2030 global goals and to assess progress on the path to CC elimination. In addition, an interim report on the progress made in the European Region for the CC elimination is planned and it will be presented to the WHO Regional Committee for Europe in 2026 (24).

Our study is in line with the guiding principles of the WHO European Region roadmap, in particular with regard to the definition of indicators for monitoring CC elimination strategies.

The importance of indicators was also emphasized in the Europe's Beating Cancer Plan. In fact, the European Cancer Inequalities Registry (25) was created to provide reliable data on cancer prevention and care to identify trends, disparities and inequalities between Member States and European regions. This registry proposes the following indicators for monitoring data on CC elimination: death rate per 100,000 women due to CC, the percentage of girls (aged 15 years old) who received a recommended dose of HPV vaccine, the percentage of women aged 20–69 who reported to have never had cervical smear test.

According to data reported by the European register, Italy is with France and Bulgaria among the European countries with the lowest HPV vaccination coverage. On the other hand, for the screening indicator, Italy in line with the European average (25).

The Australian experience and our study emphasized that attention should be paid also to other indicators to comprehensively monitor the attainment of the targets proposed by the Global strategy for the CC elimination.

Our study has some limitations. First, collected data are not updated to the last year. Furthermore, a selection bias could not be completed ruled out even though the mapping process was performed by six researchers independently and based on specific criteria. Eventually, the heterogeneity of data limits the possibility to further elaborate on information and issue more definite findings. Nevertheless, in our opinion, this first Italian regional mapping on prevention interventions for the CC control could help bringing forward the assessment and the appraisal of the health policies in this field from the point of view of both academic research and supranational, national and local decision-makers.

Conclusions

The mapping of the Italian Regions highlighted that HPV vaccination coverage and cervical screening coverage are still too low to achieve CC elimination by 2030; furthermore, an important regional heterogeneity was shown in respect to primary and secondary prevention policies, strategies and implementation status. Therefore, our study highlighted room for improvement regarding several issues, as the highlighted heterogeneity imply great differences in terms of access and equity.

The assessment of the status of achievement of vaccination, screening and treatment goals and the identification and constant assessment of specific indicators for monitoring the progress toward CC elimination are fundamental actions to be able to respond to the WHO call. To achieve the goals proposed by the global strategy for the CC elimination, all available means must be used, also in Italy, focusing on a comprehensive approach in favor of value-based effective interventions of prevention and best practices to be implemented at regional level.

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

Conceptualization and methodology, project administration, and funding acquisition: GEC. Definition of the search strategy, supervision, and data review: GEC and CdW. Search of documents on HPV vaccination and CC screening policies and strategies in Italian regions: MTR, FD'A, CC, MS, RM, and AP. Data analysis: MTR and FD'A. Writing—original draft preparation: MTR, FD'A, GEC, and CdW. Writing—review and editing: GEC, RR, RPdV, and CdW. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

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Gov→Value: How to combine reported quality experiences and patient-reported outcome measures. First results on vulvar cancer patients in an Italian Research Hospital

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Introduction: Vulvar cancer (VC) accounts for <1% of cancers affecting the female gender. Clinical Pathways (CP) and Clinical Outcomes Monitoring are useful for providing high-quality care to these patients. However, it is essential to integrate them with the patient's perspective according to Value-Based Healthcare paradigms. Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) are tools for assessing outcomes and experiences with health care from the patient's perspective. The aim of this paper is to collect and synthesize PROMs and main stakeholders' experience on the VC CP, according to a value-based approach.

Materials and methods: To select the most appropriate instrument, a review was conducted on the main databases and official websites of specific institutions and organizations. In the second phase, a 2-round Delphi survey was conducted to assess the Reported Experience Measures (REMs) tool. Questions were evaluated according to four criteria (general relevance, evidence-based, measurability, actionability) and included if strong agreement was reached. A Principal Component Analysis (PCA) was executed. Cronbach's alpha and McDonald's omega were computed. Fisher's exact test and Wilcoxon rank sum test were used to compare ratings between groups. Descriptive statistics were performed for both PROMs and REMs instruments.

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Results: For PROMs assessment, EORTC QLQ-C30 questionnaire was selected and administered to 28 patients. Global Health Status/Quality of Life and Functional Scales Scores were high or very high, while symptoms scale reported low or medium scores. The final REMs consists of 22 questions for professionals and 16 for patients and caregivers. It was administered to 22 patients, 11 caregivers, 5 physicians, 2 nurses and 1 clinical senior manager. PCA identified 4 components. Scale reliability was acceptable ($\alpha = 0.75$ 95% CI: 0.61–0.85; $\omega = 0.69$; 95% CI: 0.54, 0.82). A statistically significant difference between the patient/caregiver group and the professionals was found for items 8 (follow-up), 10 (perceived quality), 12 (safety), and 16 (climate) ($p = 0.02$; $p = 0.03$; $p < 0.001$; $p < 0.001$, respectively).

Discussion: PROMs could provide new ways of intercepting patients' needs and feedback, thus acting on them. The proposed REMs tool would allow to detect information not available elsewhere, which, through Audit and feedback strategies, could lead to enhancement of healthcare experience, according to a value-based approach.

KEYWORDS

patient-reported outcome measures (PROM), healthcare quality, oncologic care, value based healthcare, audit & feedback

1. Introduction

Over the past few decades, neoplastic diseases have increased in incidence and prevalence, becoming one of the leading causes of death. However, some cancers are not very widespread. Vulvar cancer (VC) is one example. They account for about 5 percent of all cancers affecting the female genital tract (1). The annual incidence is 1–2/100,000 women. It is most frequently diagnosed in women aged 65–74 and accounts for <1% of cancers affecting the female gender (2, 3). Nevertheless, as the average life expectancy increases, cases of VC are likely to increase. To best deal with it, a drastic change in the organization of care pathways is required.

Patients with VC require multidisciplinary evaluation to design the best personalized clinical approach (4–6). This leads diverse health professionals to work and share their expertise and knowledge to create evidence-based decision-making according to the perspective of personalized medicine.

For these reasons, most hospitals have begun looking at new organizational paradigms to reshape hospital care delivery processes, moving away from the lines of traditional academic specialties and focusing primarily on patient needs (7). This is particularly true in the oncologic field where, in a Shared decision-making (SDM) context, patients and families are becoming more active, informed, and aware of the risks and benefits of various treatment options (8).

It involves the application of methods and tools to combine physician and manager perspectives to leverage the centrality of the person cared for, shifting from a "disease-centered" to a "person-centered" approach (9).

In 2022, Fondazione Policlinico Universitario A. Gemelli-IRCCS (FPG-IRCCS), a large tertiary care center located in Rome (Italy) and one of the largest Italian Oncological Centers, set up and implemented a VC critical pathway (CP). It encompasses the optimal care processes to improve quality and ensure that every care episode follows the most updated scientific evidence (10). In addition, consistent with the best updated scientific evidence, a multidisciplinary VC team was established in our institution. Structured around a core team and supplemented by a group of support specialists and a care manager, it is responsible for treatment strategies and individualized management. In their multidisciplinary tumor board meeting, about 260 cases are discussed annually (5). Finally, during the CP design phase, key performance indicators (KPIs) were selected and calculated to monitor the overall performance of the CP and ensure continuous improvement in the quality of care through audit & feedback (A&F) strategies.

However, an understanding of the experience and perspective of patients, caregivers and healthcare professionals involved in CP is missing in this context.

According to a value-based approach, this paper aims to collect and synthesize patient-reported outcomes and main stakeholders' experience on the CP for VC patients.

Specifically, the aim is to:

1) Collect and summarize the PROMs (Patient Reported Outcome Measures) of patients within the CP;

2) Measure, through validated questionnaires, the experience of various CP's stakeholders (patients, caregivers, physicians, nurses and managers), compare and assess the concordance of their perceptions regarding the issues of safety and quality of care.

2. Materials and methods

To develop the Gov → Value tool, a three-phase methodology was carried out: extensive literature review to identify a PROMs questionnaire for patients with VC; extensive literature review and Delphi validation of a Reported Experience Measures (REMs) questionnaire; pilot study.

2.1. Literature review concerning VC PROMs

In order to select a tool for measuring PROMs specifically in the case of patients with VC, validated in the Italian language, an extensive search of the main evidence-based and already validated questionnaires in the literature was carried out.

The main databases (PubMed, Scopus, Web of Science) and official websites of institutions and organizations with specific expertise in this field (AIOM, CIPOMO, EORTC, ICHOM, Istat) were consulted.

2.2. Literature review and Delphi validation of a REMs questionnaire

In the second stage, we scoured the scientific literature to identify relevant items for our REMs questionnaire. The main databases (PubMed, Scopus, Web of Science) were consulted. Based on the results of the review, we elaborated a set of items designed to assess experience as reported by various stakeholders (patients, caregivers, physicians, nurses, senior managers). A two-round Delphi survey was conducted to validate the final version of the REMs questionnaire. During the first round, a panel of experts was asked to express, for each question, their degree of agreement on a Likert scale of 1 to 3 (with 1 corresponding to the minimum-"Not Relevant" and 3 corresponding to the maximum-"Relevant"), based on the following four criteria:

- General Relevance.
- Support from scientific evidence.
- Measurability.
- Actionability.

The average of the four scores provided corresponded to the "overall" score, which was used to exclude items from the final set of indicators. In both rounds, the indicators with the lowest scores were excluded. The second round was also used to validate the final set of indicators.

The panel selection criteria for this study included at least one of the following: (i) publications on the topic of Clinical Governance; (ii) experience on the topic of Clinical Governance; (iii) knowledge and expertise of the phenomenon of Clinical Governance; and (iv) willingness and motivation to participate. All identified experts were contacted individually and asked for their willingness to participate in the Delphi process. Eleven experts, including healthcare managers, economists, and physicians, patient organization's representatives, were recruited. The team of experts was invited to complete the Delphi survey by email, through a Google Modules questionnaire. A cover letter explained the purpose, relevance, and usefulness of this survey. The answers were collected immediately and anonymously. At the end of the study and after the two Delphi Rounds, the instrument in its integrity (including all the questionnaires) was validated.

This methodology replicated one already applied by the team to another clinical setting (11).

The first Round of consultation started on the sixth of April 2022 and ended on the twentieth of April. The authors considered the following levels of agreement:

- "Strong Agreement": "Overall" score of the item is equal to or more than 2.5 out of 3.0.
- "Agreement for Exclusion": "Overall" score for each item is equal to or more than 2.0 out of 3.0.

In the presence of a "strong agreement for inclusion", the indicator was included in the Second Round of the Survey. Items falling in the category "agreement for exclusion" were eliminated. The Second Round was structured as the First Round. For the final list of questions, the following levels of agreement were established:

- "Strong agreement for inclusion in the final list": "Overall" score equal to or more than 2.5 out of 3.0.
- "Agreement for exclusion from final list": mean of "Overall" score for each item <2.0 out of 3.0.

The Second Round of consultation started on the twenty-fifth of April 2022 and ended on the fifth of May 2022.

2.3. Pilot study

In the third stage, the final version of the Gov→Value Tool (REMs questionnaire plus PROMs questionnaire) was tested in a sample of VC patients and their care team.

The pilot study was monocentric, taking place in the FPG-IRCCS VC outpatient setting, between May and June 2022.

Patients with the following ICD-9-CM codes: 184.4 (vulvar malignant tumor, unspecified), 196.5 (secondary and unspecified malignant tumors of the lymph nodes of the inguinal region and lower limb), 196.6 (secondary and unspecified malignant tumors of intrapelvic lymph nodes), 196.2 (secondary and unspecified malignant tumors of intra-abdominal lymph nodes), caregivers, nurses, physicians, and clinical managers were recruited from the VC CP of the FPG-IRCCS. Data regarding age, co-morbidities and demographics were collected face-to-face during clinical examinations performed by the care manager.

Given the pilot nature of our study, no standard sample sizing is necessary. Rules of practice for in-house pilot studies indicate 20 patients as the minimum sample (12).

2.3.1. Inclusion criteria

All patients that are more than 18 years old and with malignant VC diagnosed on the VC CP are enrolled in the study and invited to reply to the questionnaire.

The eligible caregivers, instead, must be more than 18 years old and assist patients diagnosed with malignant VC included in the CP.

The eligible healthcare professionals (physician/nurse/manager) work in the Vulvar Pathology outpatient setting.

All the people included in the study must give the informed consent to the processing of data for research purposes.

2.3.2. Exclusion criteria

Patients who are not able to understand the questions of the questionnaire (e.g., cognitive capabilities alteration, non-comprehension of Italian language) were excluded.

The caregivers excluded are those who are not able to understand the questions of the questionnaire.

Other patients and caregivers excluded are those with no informed consent to the processing of data for research purposes, as well.

2.3.3. Survey administration

REMs and PROMs questionnaires were collected in a self-completed manner between May and June 2022. For patients unable to complete the questionnaire on their own, who expressed their willingness to participate in the study, completion support was offered, to ensure equity of participation.

2.3.4. Processing of personal data

An informative note about the study was provided to respondents. Informed consent for the processing of data was required, complying with General Data Protection Regulation, 2018. In the module for informed consent collection, the freedom of withdrawing the consent in any moment is specified.

2.3.5. Institutional review board approval

The research protocol was approved by the Ethics Committee of the Fondazione Policlinico Gemelli, Rome.

2.3.6. Data analysis

2.3.6.1. PROMs questionnaire

A descriptive analysis of the collected data was performed. The scores obtained from the PROMs questionnaires, linearly transformed on a scale from 0 to 100, were summarized and reprocessed using appropriate statistical methodologies, as indicated in EORTC QLQ-C30 manual (13). Mean, standard deviation (SD), median and interquartile range (IQR) were used for quantitative variables.

2.3.6.2. REMs questionnaire

With regard to the REMs questionnaire, for categorical variables, absolute and relative frequency were provided, whereas mean, SD, median and IQR were used for quantitative variables. The Shapiro-Wilk test was applied to test the Gaussian distribution of the quantitative variables. A scale score was calculated by adding up individual items from the REMs questionnaire. A Principal Component Analysis (PCA) was run to collapse the questionnaire variables into a smaller number of principal components accounting for a large share of variance. The PCA was based on polychoric correlations, given the ordinal nature of data. A varimax rotation was applied, thus obtaining rotated components (RCs). Bartlett's test of sphericity and the Kaiser-Meyer-Olkin test were performed to check PCA's assumptions. Cronbach's alpha (>0.7 considered satisfactory) and McDonald's omega (>0.7 considered sufficient) were computed to assess questionnaire reliability. Missing data were handled through pairwise deletion, whenever possible. In order to compare ratings between groups, Fisher's exact test was used, based on indications on individual items' comparisons (14), while Wilcoxon rank sum test was used for the total scale. Effect size was reported, as well, by means of Cramer's V and r, reported with a 95% confidence interval. Effect size interpretation was based on commonly followed recommendations in published literature (15, 16).

Values of $p < 0.05$ were considered statistically significant. All statistical analyses were carried out in R software, version 4.2.0 (CRAN®, R Core 2022) within the RStudio platform, version 2022.02.3 + 492 (© 2009–2022 RStudio, PBC).

3. Results

3.1. Literature review

3.1.1. PROMs

As a result of our literature review, EORTC QLQ-C30 questionnaire was selected (Appendix 1). It is already validated and consists of 30 areas comprising different scales, implemented to measure physical, psychological and social functions of cancer patients. The first 28 questions have four different answers: 1 = No; 2 = A little; 3 = A lot; 4 = Very Much.

The last two, instead, have a Likert scale from 1 to 7 as possible answers. The questionnaire is available at https://qol.eortc.org/questionnaire/eortc-qlq-c30/. Linear transformation was executed according to the dedicated manual (13) (Table 1).

3.1.2. REMs

As a result of the literature review, a questionnaire was defined as follows:

- Doctor: 22 questions (14 Quality; 8 Safety);
- Nurse: 22 questions (14 Quality; 8 Safety);
- Senior Manager: 22 questions (14 Quality; 8 Safety);
- Patient: 16 Questions (10 Quality; 6 Safety);
- Care manager: 16 questions (10 quality; 6 safety);

Some questions are identical, while others were reformulated considering the user of the questionnaire. 18 questions were ranked through a 4-point Likert score:1 = no; 2 = a little; 3= rather much; 4 = very much. 4 questions (items 6, 9, 10, 20) were ranked on a dichotomic basis: yes; no.

3.2. Delphi validation of REMs questionnaire

3.2.1. First round of consultation

Ten (91%) out of eleven experts recruited responded to the First Round.

The analytical results are reported by questions and by evaluation criterion (**Annex 1**).

All the sections (Physicians, Nurses, Senior Manager, Patients, Caregivers) were validated entirely in First Round and they were all included in the Second Round.

However, the "Nurses' quality Section" received the lowest scores on some items.

3.2.2. Second round of consultation

Participation in the consultation was completed by 10 out of 10 participants (100%) and considered valid.

As well as in the first round of consultation, all the questionnaire sections received a positive evaluation from the experts and were validated entirely.

The average of each dimension of each perspective is 2.7 in the Second Round.

The resulting Five-sections questionnaire is composed of 72 questions, divided as follows (**Annex 1**):

1. Physicians: 22 questions (14 Quality Section; 8 Safety Section);
2. Nurses: 22 questions (14 Quality Section; 8 Safety Section);
3. Senior manager: 22 questions (14 Quality Section; 8 Safety Section);
4. Patients: 16 questions (10 Quality Section; 6 Safety Section);
5. Caregivers: 16 questions (10 Quality Section; 6 Safety Section).

3.3. Pilot study

3.3.1. PROMs

Twenty-eight women with VC were identified during the study period, and response rate was 85.71% (N = 24). The median age was 64 (Interquartile Range = 22).

The majority of respondents were in post-treatment phase (follow-up), counting for the 95.83%.

The most frequent functional difficulties encountered by women mainly concerned their roles: they felt limited in their job (39.12%, N = 9 reported "a lot"/"very much" as level of limitation) and in their typical free-time activities (41.67%, N = 10 reported level "a lot"/"very much"). As concerns symptoms, difficulties in sleeping (39.12%%, N = 9 answered "a lot"/"very much") and weakness were common (39.12%, N = 9 answered "a lot"/"very much") and they frequently felt tired (41.67%, N = 10 answered "a lot"/"very much").

On the status of their global health (QoL), on a range of 1/7, the women in a level ≥5 for "Health in the last 7 days" were 11 (45.83%). For an evaluation, instead, of their "Quality of life in the last 7 days" 10 women (41.67%) reported levels ≥5.

Table 1 reports results of PROMs administration.

3.3.2. REMs' results

Twenty-two patients were included in the pilot study. All of the available caregivers (n = 11) accepted to respond. Physicians (n = 5), nurses (n = 2) and a clinical senior manager (n = 1), with experience in the treatment of women with VC, were also interviewed.

With regard to REMs questionnaire, mean, standard deviation (SD), median and interquartile range (IQR) of each Likert item's responses, classified into 2 categories, namely patients/caregivers and professionals, are displayed in

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TABLE 1 Results of EORTC QLQ-C30 questionnaire.

	Num. of items	Item numbers	Raw Score	Range	Linear transformation	Linear transformation color interpretation
Global health status/QoL						
Global health status/QoL	2	29, 30	4.63	6	60.51	
Functional scales						
Physical functioning	5	1 to 5	2.13	3	62.32	
Role functioning	2	6.7	2.41	3	52.9	
Emotional functioning	4	21 to 24	2.13	3	62.34	
Cognitive functioning	2	20.25	1.54	3	81.88	
Social functioning	2	26.27	1.72	3	76.09	
Symptom scales/items						
Fatigue	3	10,12,18	2.45	3	48.31	
Nausea and vomiting	2	14.15	1.46	3	15.22	
Pain	2	9.19	1.93	3	31.16	
Dyspnoea	1	8	1.57	3	18.84	
Insomnia	1	11	2.22	3	40.58	
Appetite loss	1	13	1.74	3	24.64	
Constipation	1	16	1.61	3	20.29	
Diarrhea	1	17	1.35	3	11.59	
Financial difficulties	1	28	1.48	3	15.94	

0–30 corresponds to dark red. **31–50** corresponds to orange. **51–70** corresponds to light green. **71–100** corresponds to dark green.

Table 2. As to dichotomic items, Table 3 reports absolute and relative frequency.

A radar plot summarizing mean responses provided by professionals and patients/caregivers is shown in Figure 1.

A barplot showing ratings for each item, classified by group of raters (patients/caregivers and professionals) is depicted in Figure 2.

3.3.2.1. PCA

The first 4 components accounted for 85% of variance in the dataset (Table 4). Explanation of therapy risks, visit duration, information provided, safety and shared decision-making mainly contribute to RC 1. RC 2 mainly consists of the following variables: punctuality, patient-physician climate and accessibility in terms of ease of visit reservation. Clear description of adverse reactions and polytherapy risks largely contribute to RC 3. Provision of informative material, indications on follow-up steps and facility accessibility have the highest loadings on RC 4. RC 1 can be interpreted as general care quality features of the visit itself. RC 3 is mainly concerned with the experience related to medical therapy prescription. RC 2 consists of aspects related to the visit experience, such as punctuality and physician-patient climate. Lastly, RC 4 mostly has to do with follow-up relevant activities.

3.3.2.2. Reliability analysis

When considering 13 4-point Likert items administered to all respondents (patients, caregivers and professionals), Cronbach's alpha was satisfactory ($\alpha = 0.75$; 95% CI: 0.61–0.85). McDonald's Omega was similarly sufficient ($\omega = 0.69$; 95% CI: 0.54, 0.82).

Cronbach's alpha if an item is deleted ranged from 0.48 to 0.77. Omega if an item is deleted ranged from 0.54 to 0.75. Specifically, item 7 and item 11 would increase omega notably.

When stratified by RC, Cronbach's alpha was 0.87 (95% CI: 0.80–0.92) in RC1, 0.91 (95% CI: 0.83–0.96) in RC3, 0.6 (95% CI: 0.38–0.81) in RC2 and 0.49 (95% CI: 0.14–0.71) in RC4.

When applied to the 13 4-point Likert items administered to patients and caregivers, Cronbach's alpha was satisfactory ($\alpha = 0.73$; 95% CI: 0.56–0.85), while McDonald's Omega was nearly sufficient ($\omega = 0.64$; 95% CI: 0.43, 0.80). If an item is dropped, alpha ranged from 0.37 to 0.76, while Omega was in the range from 0.32 to 0.72. Still, items 7 and 11 were negatively affecting omega the most.

Considering the 18 4-point Likert items for the professionals' group, Cronbach's alpha was fairly high ($\alpha = 0.84$; 95% CI: 0.62–0.96) and McDonald Omega was sufficient ($\omega = 0.82$; 95% CI: 0.58−0.96). Alpha ranged from 0.82 to 0.86 and omega from 0.32 to 0.87, in the case of removing an item. Deletion of items 2 and 21 would increase omega the most.

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TABLE 2 Mean, SD, median and IQR of responses to each Likert item, classified by respondent group (patient/caregiver or professional).

			Mean (SD)		Median(IQR)	
Item no.	Subject	Missing (N)	Patient/caregiver	Professional	Patient/caregiver	Professional
1	Care accessibility	0	3.52(0.87)	3.63(0.52)	4 (0.0)	4(0.25)
2	Punctuality	0	3.27 (0.88)	3 (0.76)	4 (1)	3 (0.5)
3	Information provided	0	3.7 (0.81)	3.5 (0.76)	4 (0)	4 (1)
4	Visit duration	0	3.61 (0.86)	3.38 (0.74)	4 (0)	3.5 (1)
5	Shared decision making	0	3.67 (0.82)	3.63 (0.74)	4 (0)	4 (0.25)
7	Informative material	0	2.64 (1.37)	1.63 (1.06)	3 (3)	3 (1)
8	Follow-up	0	3.97 (0.17)	3.63 (0.52)	4 (0)	4 (1)
11	Facility accessibility	0	3.06 (1.06)	2.5 (0.93)	3 (1)	2.5 (1)
12	Safety	0	3.76 (0.66)	3.25 (0.71)	4 (0)	3 (1)
13	Therapy risks/benefits	0	3.55 (0.79)	3.13 (0.83)	4 (1)	3 (1.25)
14	Adverse reaction	6	2.96 (1.26)	3.25 (0.89)	4 (2)	3.5 (1.25)
15	Polytherapy	6	2.93 (1.33)	3.38 (0.74)	4 (2.5)	3.5 (1)
16	Climate	0	3.73 (0.76)	3.13 (0.64)	4 (0)	3 (0.25)
17	Clinical outcome	0	–	2 (0.92)	–	2 (2)
18	Audit	0	–	2.88 (0.83)	–	3 (1.25)
19	Multidisciplinarity	0	–	3.13 (0.99)	–	3.5 (2)
21	Error reporting	0	–	3.13 (1.13)	–	3.5 (1.25)
22	Safety culture	0	–	2.88 (0.83)	–	3 (1.25)

TABLE 3 Percentage of responses to dichotomic items.

Item n.	Missing (N)	Levels	Patients/caregiver (%)	Professionals (%)
Item 6	2	No	1 (3.2%)	0 (0%)
		Yes	30 (96.8%)	8 (100%)
Item 9	2	No	15 (45.5%)	1 (16.7%)
		Yes	18 (54.5%)	5 (83.3%)
Item 10	1	No	25 (78.1%)	3 (37.5%)
		Yes	7 (21.9%)	5 (62.5%)
Item 20	0	No	–	3 (37.5%)
		Yes	–	5 (62.5%)

3.3.2.3. Comparison between scores from patients/caregivers and professionals

Results from comparison between professionals' and patients/caregivers' responses to each item are reported in Table 5.

A statistically significant difference between the patient/caregiver group and the professionals was found for items 8, 10, 12 and 16 ($p = 0.02$; $p = 0.03$; $p < 0.001$; $p < 0.001$, respectively). Effect size was medium for item 8 and 10 and large for items 12 and 16.

Items 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 14, 15 and the total scale show no statistically significant difference, when comparing responses from patients/caregivers with those from professionals.

A comparison between scores from each individual group of stakeholders (physicians, nurses, manager, patients, caregivers) led to statistically significant differences for items 8 ($p = 0.002$), 12 ($p = 0.003$) and 16 ($p < 0.001$).

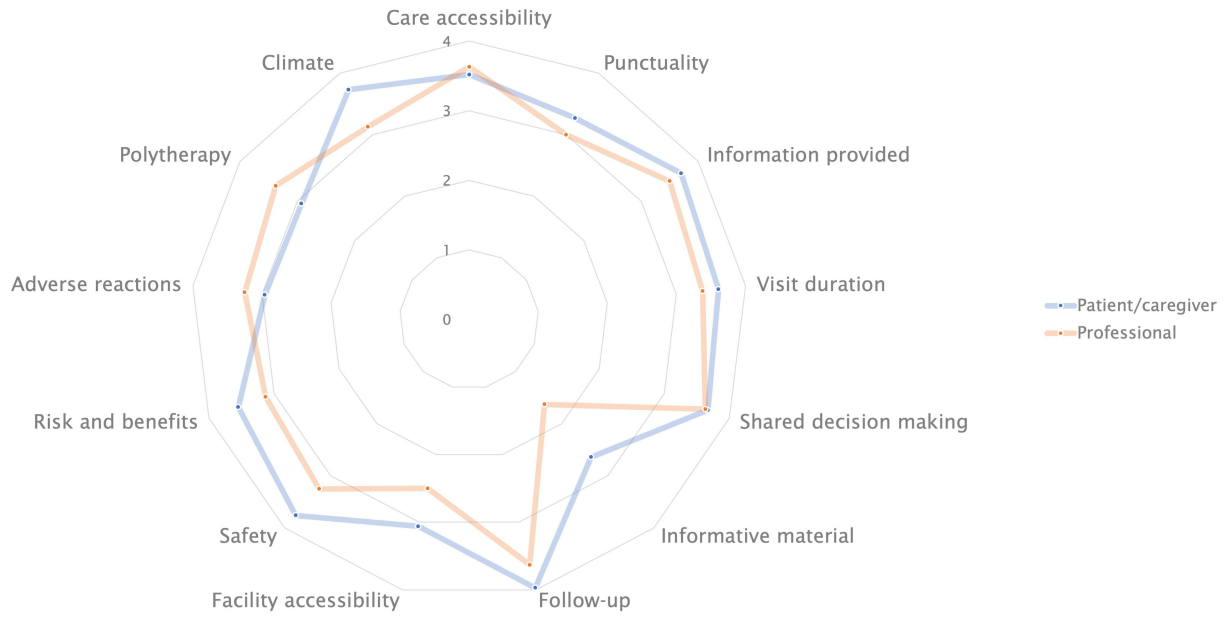

FIGURE 1
Radar plot showing mean scores for item topic, as assigned by professionals and patients/caregivers.

4. Discussion

The main goal of our research was to collect and synthesize patients' and key healthcare stakeholders' experience on a CP dedicated to women with VC, as only a few tools have been developed in oncological care to explore these items (17).

In several countries, patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) are widely used in research and performance evaluation (18). This item is crucial as healthcare organizations could use PREMs and PROMs to: (a) improve the quality of care on an individual level, *via* a patient-centered approach through the implementation of personalized care, notably due to consideration of patients' concerns and needs; (b) improve diagnosis of diseases and potentially reduce their severity, *via* more regular or systematic assessment of the effectiveness of care and monitoring of disease progression; (c) increase patient information, communication and shared medical decision-making (19), thus paving the way for precision and personalized medicine (20, 21).

The present work aims to move beyond the mere patient experience (PREM) assessment by including all the key CP stakeholders' viewpoint. By doing so, PREMs were integrated with doctors, nurses and clinical leaders and caregivers' perspective, thus becoming "Reported Experience Measures" (REMs).

As no validated questionnaires on REMs were available, a specific one was designed, constructed, validated through the Delphi methodology and administered.

The proposed tool aims to analyze the same phenomenon (comparable dimensions of quality and safety and all referred to the same care event) from different perspectives.

Such an approach would recall the application of lean tools to improve quality and safety of care in testing or diagnostics (22) by comparing quality and safety experiences based on five different perspectives. It would be a development of the "Go to the Gemba", the Japanese word meaning "go to the place" through the processes of care (23), so as to implement quality improvement initiatives where concordance among the different perspectives lacks.

To this end, it becomes essential to find organizational solutions that combine a high degree of specialization, technical and scientific advances, multidisciplinary and multiprofessional coordination, and patient participation (24).

To pursue such an approach, an internal organization consistency is required: (a) first, a standardized CP has to be developed by a dedicated multidisciplinary team to provide "case by case", high-quality diagnosis, and evidence-based decision-making in the context of personalized medicine; (b) secondly, a set of KPIs has to be defined by the hospital monitoring system. This, combined with an A&F system, creates a virtuous environment with the primary goal of improving health provider performance and healthcare outcomes.

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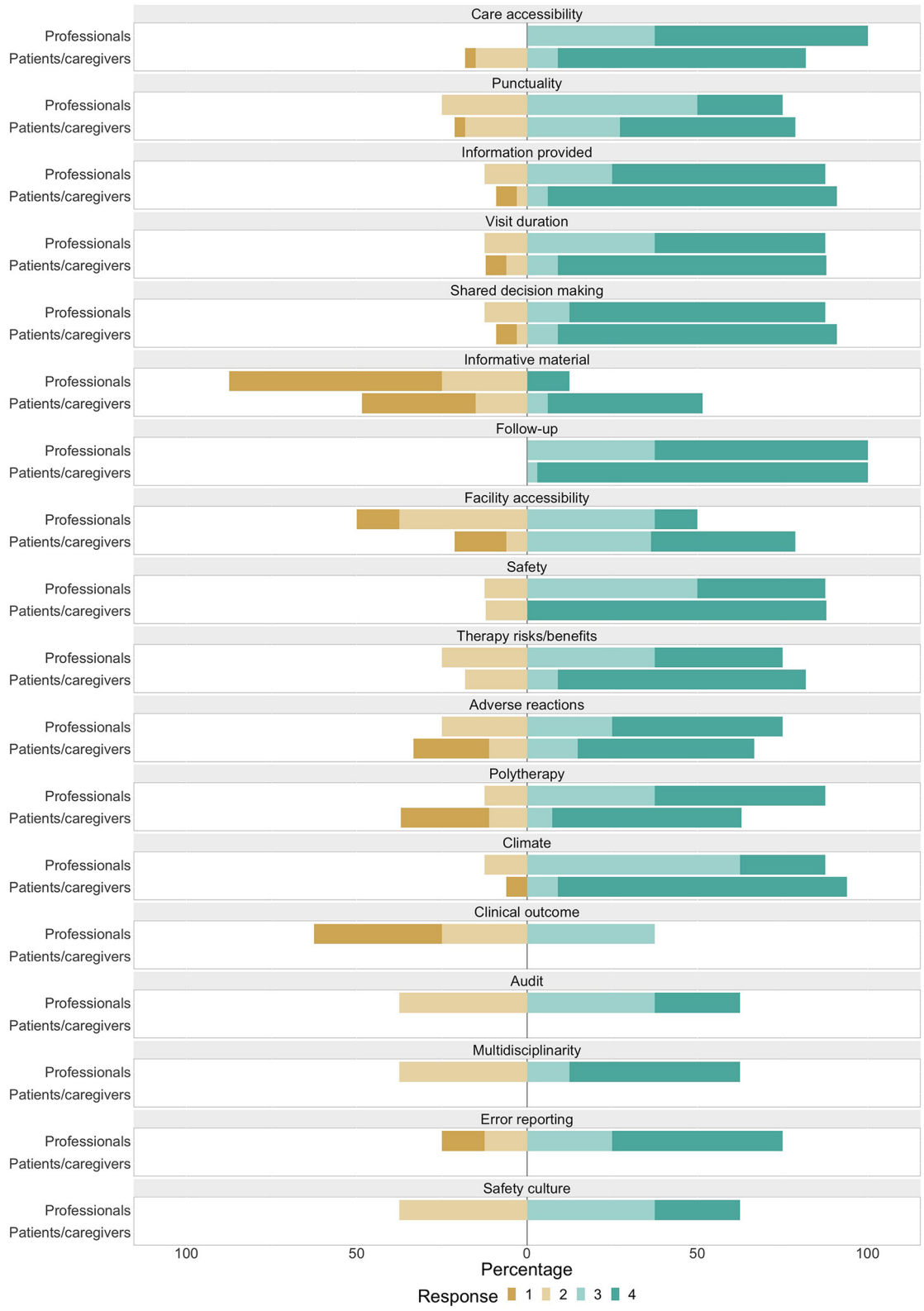

FIGURE 2
Barplot showing distribution of Likert items' responses among various scores, classified by group of raters. Scores 1, 2, 3, and 4, respectively correspond to responses: no, a little, rather much, very much.

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TABLE 4 Item loadings on RCs and cumulative percentage of variance accounted for by RCs.

	RC1	RC3	RC2	RC4
Therapy risks/benefits	**0.87**	0.05	0.34	0.18
Visit duration	**0.86**	0.28	0.30	−0.08
Information provided	**0.83**	0.40	−0.23	0.11
Safety	**0.79**	−0.02	0.06	0.11
Shared decision making	**0.73**	0.45	−0.40	0.00
Adverse reactions	0.36	**0.86**	0.23	0.04
Polytherapy	0.37	**0.82**	−0.03	0.24
Climate	0.31	−0.47	**0.72**	0.03
Care accessibility	−0.25	0.35	**0.84**	0.10
Punctuality	0.23	−0.01	**0.67**	0.27
Informative material	−0.14	0.18	0.15	**0.92**
Follow-up	0.46	0.03	0.12	**0.84**
Facility accessibility	0.09	**−0.64**	0.16	**0.62**
Cumulative % of variance explained by RCs	31	52	69	85

Loadings > | 0.6 | are highlighted in bold.

TABLE 5 Results of comparison between responses to each item from the professionals' and patients/caregivers' groups.

Item	Topic	*p*-value	Effect size (95% CI)	Effect size magnitude
Item1	Accessibility	0.23	0.35 (0.05–0.6)	Large
Item2	Punctuality	0.51	0.24 (0–0.51)	Medium
Item3	Information provided	0.16	0.33 (0.03–0.58)	Large
Item4	Visit duration	0.12	0.35 (0.06–0.6)	Large
Item5	Shared decision making	0.68	0.21 (0–0.49)	Medium
Item6	Care plan	1	0.08 (0–0.38)	–
Item7	Informative material	0.26	0.31 (0.01–0.57)	Large
Item8	Follow-up	**0.02**	0.46 (0.18–0.68)	Medium
Item9	Care pathway	0.43	0.16 (0–0.45)	Small
Item10	Perceived quality	**0.03**	0.36 (0.06–0.6)	Medium
Item11	Facility accessibility	0.09	0.41 (0.12–0.64)	Large
Item12	Safety	**<0.001**	0.67 (0.47–0.82)	Large
Item13	Therapy risks/benefits	0.08	0.35 (0.048–0.59)	Large
Item14	Adverse reaction	0.36	0.29 (0–0.57)	Medium
Item15	Polytherapy	0.09	0.42 (0.1–0.66)	Large
Item16	Climate	**<0.001**	0.65 (0.43–0.8)	Large
Scale		0.25	0.2 (0.01−0.48)	Small

P-value, Cramer's V with 95% confidence interval and interpretation are provided.

To our knowledge, this is among the first few studies assessing the feasibility of collecting data on different stakeholders' experience at a given "point of care" event, within the patient CP, so as to assess the different perspectives on crucial dimensions of quality and safety and elicit information to improve oncological care.

Such requirements matched with the management of vulvar cancer, where, unlike other oncology conditions, such as Breast Cancer (25, 26), the patient's experience has been less studied.

Alimena et al. (27), who examined PROMs in a typical clinic population of vulvar cancer patients, administered the following validated tools: the European Organization for the Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ-C30), the Patient Reported Outcome Measurement Information System (PROMIS) Emotional and Instrumental Support Questionnaires, and the Functional Assessment of Cancer Therapy-Vulvar (FACT-V) questionnaire.

In our study, as the other PRO questionnaires were not validated in Italian, we were able to use only the EORTC QLQ-C30 questionnaire, and as to REMs questionnaire, the one we defined was tested.

Our study has a number of strengths: it makes use of an innovative tool, in line with recent literature developments; it deploys a rigorous methodological approach throughout all of the study phases; it originally provides various perspectives on health care experience.

Our study, however, does not come without its limitations. First, by default, all studies on vulvar cancer patients have relatively small populations. In addition, as regards the PROMs questionnaire administration, differently from a previous study (27), in our study it was not possible to use disease-specific questionnaires because the Italian version was not available (e.g., PROMIS and FACT-V). As a consequence, we chose to use the European Organization for the Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ-C30). It is a frequently used patient-reported outcome instrument to assess health-related quality of life of patients with cancer. However, it is not designed to stratify by comorbidities.

Further limitations include the fact that, in questionnaire administration, a paper version was preferred. Paper questionnaires involve several time-consuming and costly steps. However, this choice is mainly related to the mean age of the patients that distinguish our cohort. Indeed, older populations typically suffer from low digital literacy, even though the proportion of elderly using digital technology has increased exponentially (28, 29).

The Delphi methodology was used to validate the REMs questionnaire. This methodology is used to combine expert knowledge and opinion to arrive at an informed group consensus on a complex problem. However, some methodological limitations should be taken into account (such as starting with provided material and questions may not be representative, the process tends to eliminate extreme positions and force a middle-of-the-road consensus and is also vulnerable to high dropout rates due to the large time commitment required) (30).

Both PCA and reliability analysis would benefit from a larger sample (31, 32). Additionally, we used Cronbach's alpha, which is a widely used coefficient for reliability assessment, despite a wide range of limits, largely based on hard-to-meet assumptions. We still reported it in light of its popularity, but decided to complement it with McDonald's Omega, which is recognized as more accurate (33). When comparing ratings, we considered patients and caregivers as one group and professionals as another, in order to avoid a fragmentation of our small sample, while still maintaining a focus on the main perspectives at stake. Furthermore, ideally, we should collect data on each individual care episode from the various stakeholders involved. This would allow a more comprehensive and specific interpretation of data.

In addition, we are aware that our search focused on patient experiences in the outpatient care setting within the hospital, and not on the whole pathway, as needed in cancer care.

In terms of future perspectives, longitudinally-administered PROMs questionnaires allow clinicians to keep track of clinical outcomes as reported by patients, as a valuable addition to clinical performance monitoring systems. This tool could provide new ways of intercepting patients' needs and feedback, thus acting on them. With regard to REMs, A&F practice based on results from the proposed questionnaire might play a key role in improving professional practice. Thus, our tool would allow to detect information not available elsewhere, with potential enhancement of healthcare experience for both patients and professionals, according to a value-based approach.

Our team emphasize how Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) are complementary and necessary tools to improve quality and safety.

Depending on the scores reported from individual perspectives, *ad hoc* improvement actions, such as A&F interventions, will be taken if discrepancies or critical issues emerge. If designed optimally and used in the right context, A&F can play an important role in improving professional practice.

This is especially true in the field of oncology, where it increasingly plays a leading role through the creation of SDM processes (34).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Fondazione Policlinico

Universitario A. Gemelli IRCCS. The patients/participants provided their written informed consent to participate in this study.

Author contributions

EM and CA: conceptualization, methodology, data processing, writing of original draft, and project management. AP: methodology, data processing, formal analysis, and writing of original draft. AB: conceptualization, review, editing of manuscript, and supervision. SF: data collection, review, editing of manuscript, and supervision. LG: recruitment of participants and data collection. GS, GG, and LT: review and supervision. All authors approved the contributions, read, and approved the final manuscript.

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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/fpubh.2022.1014651/full#supplementary-material

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Integration of art and technology in personalized radiation oncology care: Experiences, evidence, and perspectives

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Cancer diagnoses expose patients to traumatic stress, sudden changes in daily life, changes in the body and autonomy, with even long-term consequences, and in some cases, to come to terms with the end-of-life. Furthermore, rising survival rates underline that the need for interventions for emotional wellbeing is in growing demand by patients and survivors. Cancer patients frequently have compliance problems, difficulties during treatment, stress, or challenges in implementing healthy behaviors. This scenario was highlighted during the COVID-19 emergency. These issues often do not reach the clinical attention of dedicated professionals and could also become a source of stress or burnout for professionals. So, these consequences are evident on individual, interpersonal, and health system levels. Oncology services have increasingly sought to provide value-based health care, considering resources invested, with implications for service delivery and related financing mechanisms. Value-based health care can improve patient outcomes, often revealed by patient outcome measures while seeking balance with economical budgets. The paper aims to show the Gemelli Advanced Radiation Therapy (ART) experience of personalizing the patients' care pathway through interventions based on technologies and art, the personalized approach to cancer patients and their role as "co-stars" in treatment care. The paper describes the vision, experiences, and evidence that have guided clinical choices involving patients and professionals in a co-constructed therapeutic pathway. We will explore this approach by describing: the various initiatives already implemented and prospects, with particular attention to the economic sustainability of the paths proposed to patients; the several pathways of personalized care, both from the patient's and healthcare professional perspective, that put the person's experience at the Gemelli ART Center. The patient's satisfaction with the treatment and economic outcomes have been considered. The experiences and future perspectives described in the manuscript will focus on the value of people's experiences and patient satisfaction indicators, patients, staff, and the healthcare organization.

KEYWORDS

radiotherapy, technology, art, digital, personalization, oncology, engagement, patient-centered care

1. Introduction: Integration of art and technology in personalized radiation oncology care

Cancer diagnosis exposes patients to traumatic stress, and sudden changes in daily life, in body and autonomy, with even long-term consequences; some of them have to deal with the end-of-life phase (1). Over the last three decades, cancer mortality has shown an important decline, especially in most high-income countries, reflecting improvements in cancer prevention, diagnosis, and management (2). The rising of survival rates underlines also a growing need for interventions to improve patients' emotional wellbeing (2). As a fact, cancer patients frequently have difficulties during treatment, such as anxiety, depression, and stress (3, 4). These issues affect adherence to treatment, cancer survival, and treatment costs (5). Among oncological treatments, radiotherapy (RT) requires an everyday burden, often worsened by concomitant chemotherapy (4, 6, 7). The duration of treatments and the possible side effects are challenging for every oncological patient (8, 9). These are long-term treatments performed mainly on an outpatient basis, often making patients prone to show emotional discomfort (4, 6, 7).

During the last years the importance of complementary psychological support therapies in alleviating cancer patients' distress, depression as well as fatigue, and pain, has been demonstrated (10–12).

Among creative therapies, art therapy is assuming an increasingly important role in improving communication, awareness, and patient quality of life (QoL) (13). Art therapy is a form of psychotherapy that uses the expressive qualities of the visual sign in the context of a therapeutic relationship. This is meant to bring about personal change to increase wellbeing and psychological functioning (14–16). A recent systematic review (17) highlighted that, even if the mechanisms of these beneficials are still unclear, art therapy is motivating, deepens understanding, insight, and mastery, and also provides a safe and structured pathway for self-awareness (17). It also alleviates physical suffering and improves coping skills by increasing feelings of energy (15, 18). Of course, art therapy does not replace standard medical treatments. Rather, it should be integrated into a personalized, multidisciplinary approach that recognizes the role of the mind in influencing the body, promoting wellbeing and stimulating coping skills in stressful situations.

Nowadays, a significant change is taking place highlighting a patient-centered care pathway instead of a discipline-centered one (19, 20). In this scenario, several initiatives have been developed to improve patient-centeredness in cancer care (21, 22). In particular, strategies have been adopted worldwide to ensure respect for patient preferences, emotional support, physical comfort, information/communication needs, care coordination, family and friends' involvement, and access to care (23).

According to Gemelli ART (Advanced Radiation Therapy) experience, we believe that cancer patients' deepest and often unrevealed aspirations are to be cared for. Each patient is welcomed as a person living the experience of disease, potentially disabling body and soul. Technology is a tool that, under the guidance of the knowledge and expertise of our Center professionals, focuses on meeting those needs: treating the patient and taking care of the person. Thanks to the use of artificial intelligence (AI) and advanced medical technologies, it is increasingly possible to realize personalized and tailored cancer care pathways (24, 25). In our context, we are investigating the combination of art and technology to include patients' emotional and relational experiences. At this stage, we are studying how to implement at our best interventions based on art and technology on patients, staff and caregivers and how this implementation could impact their sense of involvement and care satisfaction. These dimensions often have an impact on treatment and care compliance. The impact of these variables on treatment tolerance and other clinical outcomes could be investigated in the future.

This article then aims to report the experience of our Center, where a large number of interventions that merge art and technology have been undergoing for 10 years already. This experience systematically integrates digital technology and the beauty of art into the basic standard of cancer care to provide an holistic answer to cancer patients clinical and human needs. If "Value-based medicine" is defined as the "practice that incorporates the highest level of evidence-based data with the patient-perceived value conferred by health care interventions for the resources expended" (4–6), we strive for such integration of art, technology and patient needs to lead to better personalization of treatments and, where possible, also to a positive economic impact on the National Health System.

2. Art, creativity, and technologies in cancer treatment: The Italian experience of Gemelli ART

In the following section, according to the template of the approach described above, we will describe some interventions that took place in our Center over time, involving patients and staff. Some of these projects have become multi-center experiences. The Gemelli ART Radiation Oncology department provides patients with technologically advanced instruments (ART as Advanced Radiation Therapy) and a multidisciplinary team. This center is made up of an Operating Sector with RT bunkers (4 cone-beam CT linear accelerators, 1 MRI-linear accelerators), an Interventional Oncology Center for Interventional Radiotherapy (brachytherapy), outpatient clinics for medical visits and psychological support service, a Day Hospital and two Inpatient wards. Gemelli ART, however, also stands for Art because it involves welcoming environments, exclusively decorated therapy rooms and a stunning mosaic that enriches patient's journey within our Center and offers relief through the beauty of art.

2017 - The value of patient experience

2.1. Patient's satisfaction in quantitative measures in the RAMSI project

Following the slogan: *"Technology at the service of knowledge, knowledge at the service of the patient,"* the aim is to provide healthcare services based on dynamic mechanisms focused on the patient and the quality of services. Improving healthcare quality is often reflected in clinical outcomes and patient satisfaction but it also has to consider the costs of the services offered. Patient satisfaction is recognized as a key performance indicator for monitoring the quality of hospitals (26). Through systematic analysis of patient-relevant data,

decision-making processes can be tailored to patients, empowering them to engage with healthcare systems, maximizing their health and wellbeing, and thus minimizing attrition (27).

The RAMSI *Radioterapia Amica Mia* (Radiotherapy My Friend) *Smile In*^{TM} (SI) project has foreseen the placement of SI totems with four push buttons using the HappyOrNot technology (RetailIN, Cesano Maderno MB, Italy: https://smilein.it) in our RT department. It has enabled the collection and analysis of patient feedback in the form of self-reported experience in real-time (27). Physical SI totems were installed in places of greatest affluence to promptly detect patients input and collect data on their experience during RT using HappyOrNot technology. Specifically, these locations were identified as: waiting rooms for clinics and treatment rooms, the access points and exit from the treatment rooms, and the RT service. Patients read the allocated question in the question sheet holder and gave their feedback anonymously by touching a smiley button (Figure 1). Four different faces define four assessment points: "very positive," "positive," "negative," and "very negative". To assess patient's needs and experiences, four areas of interest were defined:

- Patient-centric welcome perception: The perception of human and environmental welcome during clinics and treatments;
- Punctuality: Visits and treatments time adherence to planned schedules;
- Professionalism: Healthcare workers' competence or skill expected;
- Comfort: Environmental and human capability to accomplish patients' needs.

The RAMSI project effectively puts the patients at the center of the therapeutic process as a person in their complexity to preserve their QoL and human dignity during the radiation treatment. Furthermore, it provides a fast, easy-to-use tool to extract patient satisfaction data.

2.2. Patients' quality reports: The HAPPY protocol (Humanity Assurance Protocol in interventional radiotheraPY)

In clinical settings, as well as in oncological field, the decision-making process of treatment pathway is based on the interaction between physician and patient. However, cultural factors influence patients perceptions of the disease and treatment choices, often conditioned by factors such as age, socioeconomic status, education level, language, geographical area of origin (urban or rural), spirituality, sexual orientation, or occupation (28, 29).

The patient's psychological state is often added to the context described above. Often, anxiety and depression can reduce compliance with treatment and affect the clinical outcome (30, 31).

Based on that evidence, our Interventional RT Department proposed a study to investigate the lack of knowledge regarding needs and expectations of gynecological cancer patients and to hypothesize solutions to improve patients' emotional state and sensitivity.

To achieve this objective, the importance of each professional figure who comes into contact with the patient during the therapeutic pathway was considered, as each staff member can contribute to improving patient's management. Among the figures involved we can find physician, considering the importance of providing clinical Information for the management of symptoms, the psychologist to provide psychological support, nurses and Radiation Therapy Technologist (RTT) for the reception and reassurance of patients during treatment. The whole team contributes significantly in helping patient to better cope with the disease (20, 32–37).

We examined needs, values, expectations, and preferences among gynecological cancer patients. A specific focus was dedicated to communication and the need for information regarding therapy efficacy, side effects, and toxicities, analyzing collected data to generate working hypotheses. The second objective of this work was to propose a series of interventions/recommendations to ensure a sensitive approach to fostering the patient's psychological wellbeing during interventional Radiotherapy.

The project, which considered a sample of 30 gynecological cancer patients, was conceived and carried out within the study group of brachytherapy, interventional Radiotherapy, and intra-operative Radiotherapy (IORT) of the Italian Association of Radiotherapy and Clinical Oncology (AIRO Associazione Italiana di Radioterapia ed Oncologia Clinica).

A multi-professional team was chosen to assess the needs using a multidimensional approach composed of 1 interventional radiologist, one geriatric oncologist, one nurse, one psychologist, one radio-oncology resident, and 1 RTT. Each member of the multi-professional team performed several independent multidimensional conversations with the patients. Each patient had six different discussions, for a total of 180 talks. After this phase, the multi-professional team scheduled two meetings, the first to collect all the needs coming from the patients and the second to finalize the classification by selecting the most represented needs as a result of the 180 multidimensional conversations.

The results of the task group were submitted to an Expert Team of four physicians from 4 different institutions for a final evaluation. Both teams discussed patients needs to generate a list of interventions/recommendations aimed to address each individual need to achieve their inner wellbeing. Finally, a Master Team carried out an independent check of the project and approved it.

The list of interventions identified was HAPPY (Humanity Assurance Protocol in interventional radiotheraPY) and consists of a protocol that can be exported to other centers to guarantee humanity and the best quality of care and compliance to treatments.

Among the recommendations highlighted there is the possibility of using simple language or alternatives to terms such as brachytherapy or bunkers, which can cause more significant anxiety, as well as the possibility of creating a more welcoming hospital environment with colors or images designed to ensure a warmer and more familiar territory. Music therapy can also help manage anxiety, as favorite music can stimulate the relaxation response by activating the parasympathetic system, restoring the balance of the autonomic nervous system (38, 39).

2018 - Customized "targets" for young patients

2.3. Psychological, art, and digital interventions for pediatrics: The RADAR project

Special attention has been paid overtime to young patients. In pediatric RT, obtaining the cooperation necessary for the preparation

FIGURE 1
RAMSI project totem.

and administration of treatment is particularly complicated, as it is challenging for a child to stand still and alone (40, 41). When patients are unable to maintain a fixed and reproducible position (42), sedation or general anesthesia (GA) becomes necessary (43). In general, RT children and adolescents undergo several changes in their lifestyle (41), daily, school, and social activities (44); changes and stress are more significant in the case of GA, also due to fasting. Furthermore, the use of GA may increase the risk of medical complications (45) and impact healthcare costs (45, 46). Different studies have described the benefit of combining psychological support interventions with standard therapies to reduce the number of sedations (45, 47, 48). It has been demonstrated that a multidisciplinary approach implemented by a specialized team (49) can identify patient's needs and allow targeted interventions to facilitate treatment preparation and improve patient compliance, thus avoiding sedation when possible (46, 50–54). There are many different interventions and approaches used to reduce anesthesia, increase compliance and improve the experience of pediatric cancer patients undergoing these types of procedures (40, 45, 53, 55–57).

Our Center has recently provided an annually average of 140 pediatric treatments. The care path based on a bio-psychosocial approach was carried out by a dedicated multidisciplinary team of doctors, nurses, technicians, psychologists, and anesthetists. The RADAR project was born to increase the personalization of pediatric RT through a multidimensional approach. The project found its inspiration from a marine setting reproduced by an artist on the walls of the treatment room (Figure 2).

The project uses assessment tools, such as the Multidimensional Assessment for Pediatric patients in Radiotherapy - MAP-RT schedule (58), age-appropriate psychological preparation and psychological support, creative activities, and digital tools. All these interventions increasingly try to put the patient/family at the center by fostering engagement and co-creation processes in RT.

Among RADAR's many activities, one of the most appreciated interventions by patients/parents is an intervention based on the principles of the token economy (59–61); this method has already proven its effectiveness in other contexts (62–64). Over the last 4 years, we have built an autonomous system on understanding the feasibility of a method based on the principle of reward and "reward" in RT.

We called it "the Dreams Chest," and it offers pediatric patients the opportunity to choose online a present to receive on the last day of their therapy. According to this program, the daily RT sessions are considered a "token" to reach the treasure. The final goal represents the child's dream, although, within a fixed budget, the object takes

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FIGURE 2
Pediatric radiotherapy, any RADAR pathway' images and tools.

on a personal value because it is personally chosen. More than 400 children had the chance to express their dreams through this project, thanks to many donors and large and small companies who paid for their gifts.

"The Dreams Chest" seems an economically sustainable method that can help increase adherence to RT in pediatric patients. Overall, since the start of the RADAR project, the use of anesthesia procedures has been significantly reduced, resulting in lower healthcare costs. Since 2018, when the experience began, the number of sedations fell from 19 to 13%, which in economic terms corresponds on average to 45.000€ per year. Among the childcare monitoring tools, and after translation and cultural Italian adaptation, we have subsequently included the Parents PedsQL™ Healthcare Satisfaction Hematology/Oncology Module, to assess the level of General Satisfaction, Information, Inclusion of Family, Communication, Technical Skills, and Emotional Needs.

2019 - From needs to building

2.4. MISSION: Multisensory Integrated SyStem for patIent cOmpliaNce improvement

The MISSION project was realized from the information that emerged both from the HAPPY protocol experience and from the feedbacks we received from patients Considering the results of the study, multisensory domotic equipment (sound/music, aromatherapy, chromotherapy, images) was subsequently installed in our Interventional Oncology Center IOC (Figure 3) to improve patients tolerance to treatments through a global approach (MISSION: Multisensory Integrated SyStem for patIent cOmpliaNce improvement). We are collecting preliminary results, but in clinical practice, the intervention is already proving effective in generating a widespread sense of calm and a better management of patients' anxiety.

2020 – Gratitude staff members' intervention

FIGURE 3
Interventional oncology center room (MISSION: Multisensory Integrated SyStem for patIent cOmpliaNce improvement).

2.5. The digital group "Seeds of Gratitude"

In a person-oriented service, the needs of the people attending it are as important as those of the operators providing care. The aim is to enhance the aspects of the operator-patient relationship through attention to the relational and overall dimension of the person. Staff training courses and events on good interaction with patients are widespread; less attention is paid to interventions aimed to the wellbeing of groups and individual team members. The psychological wellbeing of healthcare workers in oncology has always been a critical issue due to the daily management of complex topics such as death and workload, resulting in a usually very high level of burnout (65). The impact of the COVID-19 pandemic on cancer patients was high in terms of anxiety, fear, and psychological distress (66). Medical staff from frontline wards, especially oncology units, was at increased risk of infection and burnout (67). Healthcare workers had to manage many challenges (68) and their psychological needs are increasingly important (69). In Italy, the emergency required timely interventions (70), especially in team working, which is crucial in multidisciplinary teams such as RT (71).

Literature in psychosocial sciences has shown that stress (72), fear (73), or emergency (74), influence human relationships; research shows that sense of belonging to the group and contact with others' emotions (75) play a central role in reducing these risks (76). Studies suggest that workplaces aiming to increase job satisfaction can do so through well-organized gratitude interventions (77). Gratitude is also related to wellbeing, and it can become helpful for healthcare professionals to relieve fatigue and restore meaning to their work (78). Therefore, during the lockdown, it was created a gratitude-focused "inter-group contact" tool (79) to increase group identity and mutual trust, rediscovering the pleasure of being part of a team. The project was conducted from April 2020, during the COVID-19 Italian lockdown.

This project consisted of a WhatsApp broadcast, in which a daily message mainly in JPEG format was published: creative cards composed of letters, emails, images, music, or videos accompanied by a short reflection (Figure 4). Patients' gratitude-oriented messages can help workers find a sense of gratification. In May 2020, when phase two started in Italy, the participants were surveyed on their satisfaction with the project (80). The results showed that 87.9 % of the staff members were satisfied with the experience ($\geq$7 out of 10) and 89.6 % expressed that they would like to continue the experience; the activity is still active with one message per week. This experience could be extended to other units. The impact on the sense of cohesion and stress reduction could be investigated in the future.

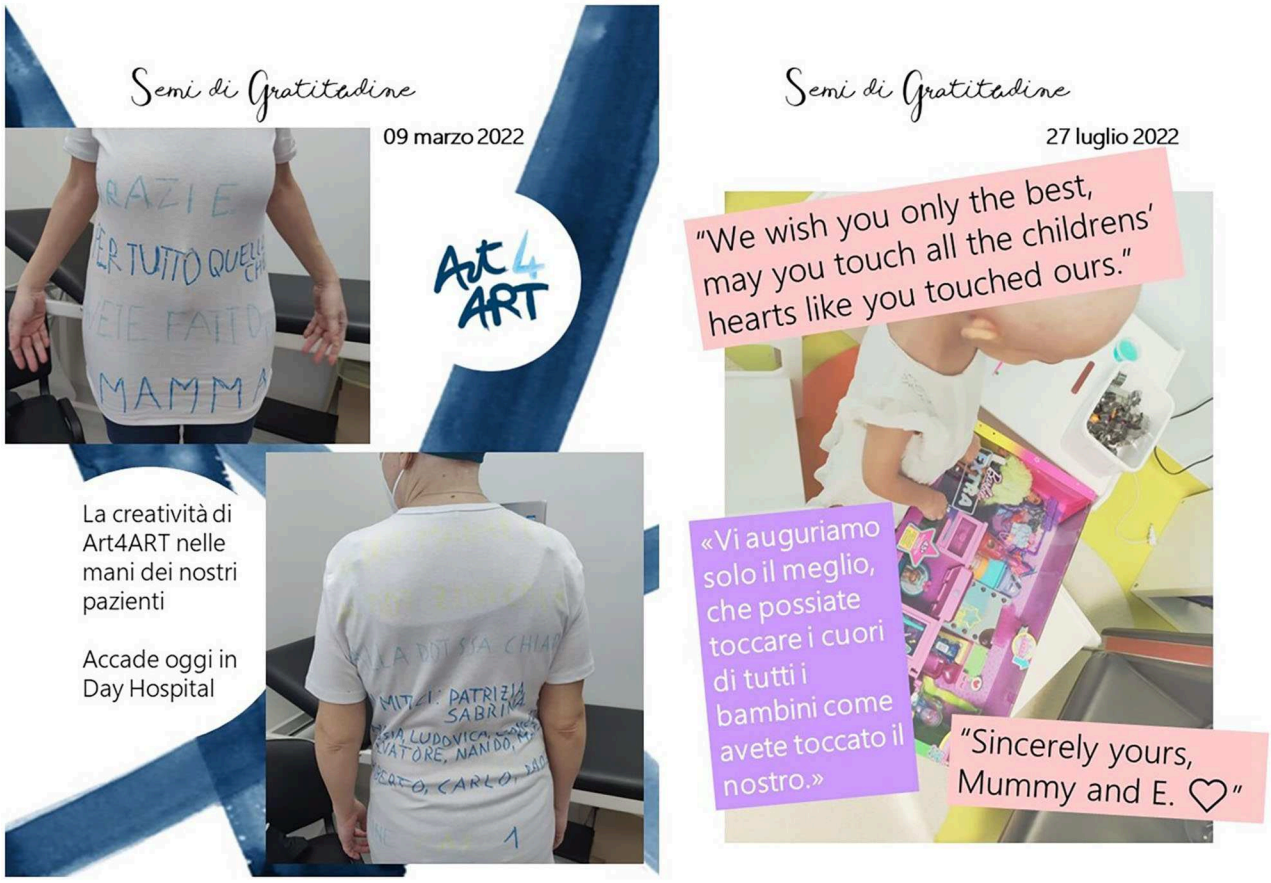

FIGURE 4
CTwo of 180 "Seeds of Gratitude" realized for the broadcast. Translation of the "Seeds of Gratitude": "thanks for what you did for mum"; "the Art4ART creativity in the hands of our patients, it happens today in day hospital"; "we wish you only the best, that you may touch the hearts of all children as you have touched ours".

"Seeds of Gratitude" also became an online book (81).

2021 - The art and technology paradigm in plan and platform

2.6. The Art4ART project

Thanks to previous experience, the architectural renovation of one of the areas of the Gemelli ART led to the birth of the Art4ART Project (7), which was able to realize the renovation of the rooms starting from a theoretical framework. Thus, in 2021 the new Art4ART Unit was inaugurated.

In addition, the physical spaces of the center were collected into a web-based digital Art4ART platform. The platform provides patients with artistic content. It is not only an entertainment opportunity, but it represents a tool that allows emotional profiling of the patient. Data regarding patients' preferences and choices are stored and analyzed in a clinical research protocol also using AI algorithm to measure and predict impact indicators regarding:

- Patient compliance
- Clinical outcomes in terms of toxicity and survival outcomes
- Psychological profile among the several diseases.

Through the systematic acquisition of patient preferences and integration with other clinical parameters, some studies are ongoing to measure the clinical, psychological, organizational, and social impact of the Art4ART project. The use of digital technology will lead to the reversal of viewpoint from *therapeutic acts* to *patient-centered care*. Art4ART will offer an art-based digital supporting patients resilience and a research platform about the role of humanities as a cure in RT.

2.6.1. The Art4ART project aims to

- Offer cancer patients undergoing RT the opportunity to enjoy several personalized artistic options to improve quality of life, compliance, efficacy, safety, and perceived quality of care.
- Use AI tools to profile patient preferences, integrate clinical data, and monitor through appropriate personalized interactions the use and benefit of the platform. This will be possible by administering on the platform psychometric psychological scales (7).
- Transform well-known international artworks and dedicate artists' productions to therapeutic tools for patients and dynamics exchanges with donors that would like to support assistance and research.

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FIGURE 5
Multimedia immersive room use during chemotherapy.

FIGURE 6
Details of the common areas of the Art4ART unit.

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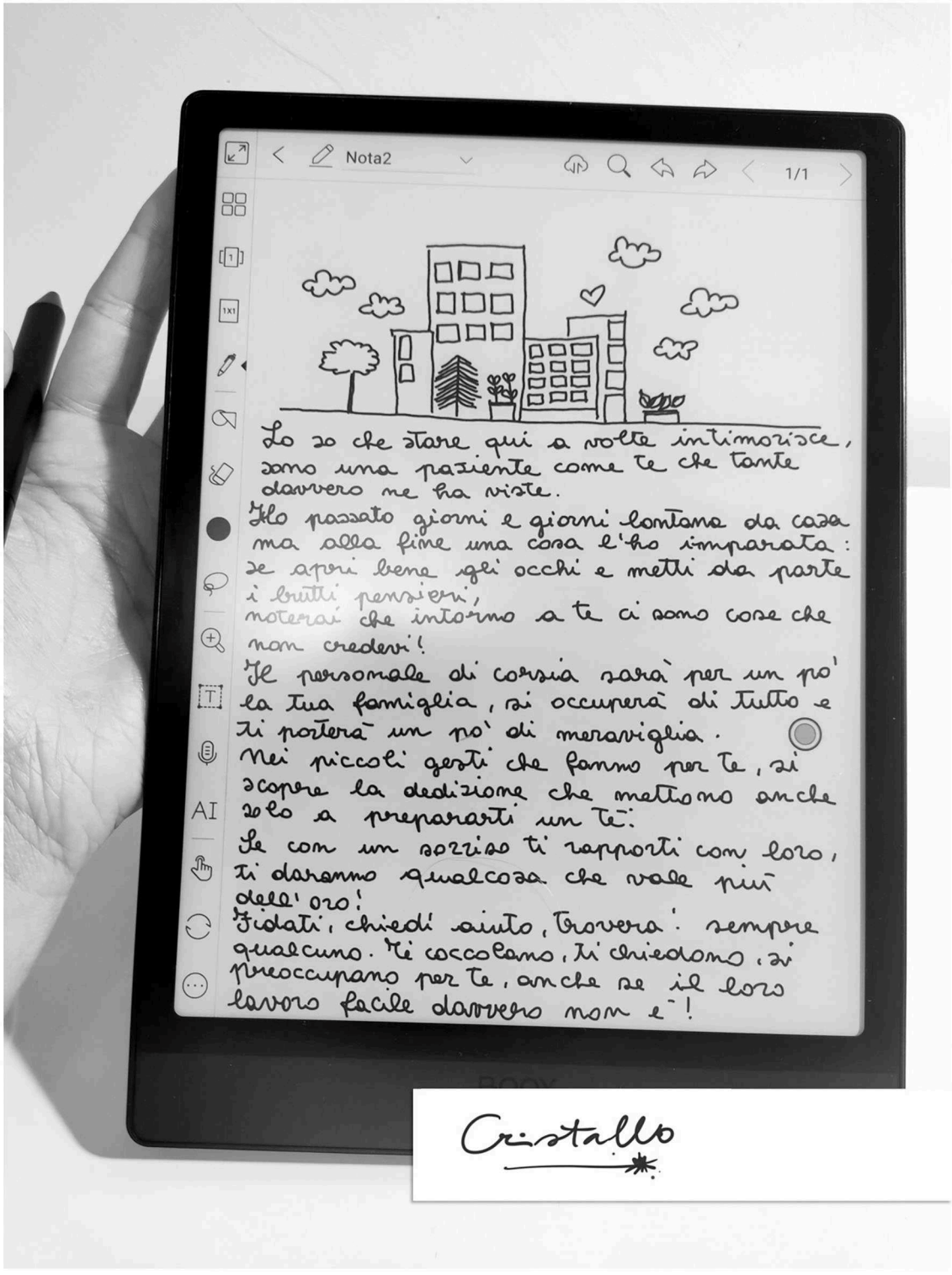

FIGURE 7
A patient's poem written on one of our Cristallo devices. Translation of the poem: "I know that being here is sometimes intimidating, I am a patient like you who has seen a lot. I spent days and days away from home, but in the end, I learned one thing: if you open your eyes wide and put aside your bad thoughts, you will notice that there are things around you that you did not believe! The ward staff will be your family for a while, they will take care of everything and bring you some wonder. In the small gestures they make for you, you will discover the dedication they put into even just making you a cup of tea. If you deal with them with a smile, they will give you something that is worth more than gold! Trust me, ask for help, you will always find someone. They pamper you, they ask you, they care for you even if their job is not at all easy!".

2.6.2. The Art4ART project tools and metrics

1. A web-based digital platform, Art4ART, has been developed to propose and share with patients several forms of art, such as video entertainment. Classifying each content according to eight human dimensions (friendship, love, attention, courage, self-care, enthusiasm, passion, and spirituality) and eight artistic channels (music, poetry, literature, cinema, nature, painting, sculptures, monuments, photography, profession).
2. A multimedia immersive room (Figure 5), where the patients during treatments can experience a 360° vision of video entertainment or several dedicated immersive experiences.
3. An art-based welcoming of the patients with an architectural and semantic metamorphosis of the treatment places: the concept of the *waiting room* has evolved toward a *welcome room* for patients called 'Odeon' according to the ancient Greeks' idea of art-dedicated theaters, with an 8-meters HD screen and a full-wall fresco painting (Figure 6). An ordinal number no longer identifies the chemotherapy infusion seats, but they are characterized by the name of a flower whose color they bear.

2022 – Tailor-made interventions and applications

2.7. Frail patients, the *Cristallo* project

Through the architectural renovation of the Art4ART inpatient unit and the combination of art and technology, we could design special care for frail patients in 2022. After the restrictions of COVID-19, considering the high psychopathological risk of the general population (82), we desired to pay attention to the physical and psychological impact of isolation and stress on cancer patients (83–85). Although the data are still few and partial, the oncology population, and their caregivers (86), are at risk of severe anxiety, stress, and depression (66, 67, 87) and long-term sequelae.

It is plain to see that different clinical conditions, treatment phases, and other clinical variables could encourage resources and coping strategies for oncological disease and therapies. In this scenario, the importance of a psycho-physical profile early assessment, especially in frail patients (older or with poor performance status) who have to undergo RT, could help healthcare professionals to identify high-risk situations and to perform a tailor-made treatment (88).

For these reasons, enhancing patient assessment and clinical monitoring during treatment reveals itself to be of essential importance. This type of early intervention could lead to the early identification of patients with possible psycho-physical frailties, personalization of care pathways, and supportive interventions, during hospitalization and after discharge.

One of the most discussed issues in the approach to the management of cancer patient is his frailty/complexity (89). By now, most new cancer diagnoses are made in patients over 70, where it is often possible to observe patients undertreatment or overtreatment (90). It is possible to keep a similar scenario in younger but frail patients or complex patients (91). Due to comorbidity, polypharmacotherapy, and social/economic network changes, those patients may have lower compliance to treatments or greater susceptibility to related toxicity treatments, The "Cristallo" project was in fact developed to overcome these problems and thanks to technological implementations in the environments This project focus on frail or complex patients for whom personalized management is essential. A therapeutic choice weighed on the patient's performance, a multidimensional approach to all comorbidities, and the patient's polypharmacy. The goal is not personalized but a tailor-made treatment designed for the patient in front of us. The Cristallo project uses a specific path from the outpatient clinic to any acute hospitalization. It follows the person with a new cancer diagnosis in various settings for cancer treatment, using geriatric oncology scores for the assessment and supportive care to manage related toxicity treatments.

In the Cristallo project scenario, a feature is represented by preserving the person's practical skills as objects contact or touch and maintaining self-sense. This is achieved through the use of graphic devices (Figure 7) that allow the preservation of one's proprioception, handwriting, and body perception.

3. Discussion

The implementation of art and digital technology in a value-based perspective can contribute to the mutual integration between cancer patient's pathway and valorisation of the patient's perceived value (92–95). The physician-doctor gap (96) has led us to reconsider in terms of "patient proximity" technological innovations such as data mining (97–101), process mining (102, 103), omics-based predictive models (104–113), patient telemonitoring, patients' communication and e-health (114, 115). These innovations can also enhance the patient's compliance and allow a better patient experience (80, 116). In several studies, including randomized clinical trials, the impact of digital technology for patient monitoring during oncological treatments was found to be effective in increasing survival outcomes (117, 118), in prevent recurrent emergency department visits (119, 120) and in improving patients physical functions, symptoms control and quality of life (121). The opportunity of reducing cancer-related toxicities represents an exciting perspective not only on the clinical-scientific and ethical side but also from an economic perspective. Indeed, cancer-related toxicity costs' are well known in literature (122). Ashmore et al. emphasized that digital technology should also be used to maintain contact with the facility also between the end of care and the subsequent follow-up when the toxicity may occur or exacerbate (123). This participatory design and co-creation mode is also considered central to ensuring equity in digital health intervention (124, 125). Bhargava et al. (126) confirmed the possibility of cost reduction through digital technology introducing a digital remote symptoms self-reporting application. The economic saving was over 62,000 dollars in a pilot study with 13 patients affected by cancer and receiving palliative care (126).

In our Center, structural, logistic, and psychological interventions merging art and technology have been implemented in the last years. This experience integrates digital technology and the beauty of art into the standard of cancer care to provide a holistic approach to cancer patients.

The use of art therapy in cancer care is a strategy that has been explored in recent years (13, 15, 18). Although there is no conclusive evidence of improved survival outcomes on randomized clinical trials

(13, 18), the feedback from patients in small case series makes us consider this approach interesting (15). The interoperability between personalized artistic proposal offered through digital devices and the hospital's electronic medical records (EMR) give us the possibility to include also those data in our clinical studies. To date, the introduction of art as a communication channel has raised awareness among supporters and sponsors of our Center.

Digital technology, like every technological innovation introduced in the healthcare sector, also requires dedicated education and training of both healthcare and administrative staff (127–129). The effectiveness of digital education interventions in different health care disciplines has been recently reviewed (130). Most studies focused on health professions education in general, surgery, and nursing. The main modalities are virtual reality and online education (130).

Recently, based on the need for an ethics evaluation that keeps the person at the Center of each technology, a new topic has been introduced, namely *algor-ethics*. It approaches the view of considering new technologies as tools for humans and preventing the possibility that they become opportunities for imbalance, disparity, or even damage.

The decision to dedicate technological innovations to support the patient in the treatment pathway by synergizing communication with the patient can open the frontiers of a "new digital humanism". In this "new humanism" technology represents a tool in support of the "human part" (131–133) opening the field of the human guided digital health in oncology.

The integration of digital technology with artistic proposal during medical and radiation oncology treatments is the fascinating challenge we decided to take on. Next steps and future perspectives are represented by the systematic measure of the impact of such technology in term of clinical outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Comitato Etico, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome Italy. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

CC, LD, VV, MG, and LT proposed the work. CC, EM, LD, PC, and SS organized and collected the material and wrote the first draft of the manuscript. SC, FB, and SB revised and corrected the draft. CC, LD, EM, PC, and GC wrote supplementary sections of the manuscript. GC, DC, LT, VV, and MG revised the last version of the manuscript and offered clinical experience in the field. AS contributed to the language review. All authors contributed to manuscript revision, read, and approved the submitted version.

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.

The reviewers declared a shared affiliation with the authors LD, EM, SC, PC, FB, SB, GC, DC, MG, VV, and LT.

Publisher's note

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Cost-effectiveness analysis of durvalumab plus chemotherapy as first-line treatment for biliary tract cancer

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Objective: The TOPAZ-1 trial reported a significant survival benefit of durvalumab in combination with chemotherapy for the first-line treatment of biliary tract cancer (BTC). However, no studies have evaluated the economics of this treatment option. The aim of this study was to assess the cost effectiveness of durvalumab plus chemotherapy compared to placebo plus chemotherapy from the perspective of US and Chinese payers.

Methods: Based on clinical data from the TOPAZ-1 trial, a Markov model was developed to simulate 10-year life expectancy and total healthcare costs for patients with BTC. The treatment group received durvalumab in combination with chemotherapy and the control group received placebo plus chemotherapy. The primary outcomes analyzed included quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs). Uncertainty in the analysis results was assessed by sensitivity analysis.

Results: For US payers, the placebo plus chemotherapy group had a total cost of $56,157.05 and a utility of 1.10 QALYs, while the durvalumab plus chemotherapy group had a total cost of $217,069.25, a utility of 1.52 QALYs, resulting in an ICER of $381,864.39/QALY. For Chinese payers, the ICER of durvalumab plus chemotherapy group was $367,608.51/QALY. Sensitivity analysis showed that the analysis was most sensitive to the price of durvalumab. For US and Chinese payers, under the respective willing to pay thresholds, the likelihood of the durvalumab plus chemotherapy arm being cost-effective was 0%.

Conclusions: Both in China and in the US, durvalumab in combination with chemotherapy is not a cost-effective option for the first-line treatment of BTC compared with chemotherapy.

KEYWORDS

cost-effectiveness analysis, durvalumab, biliary tract cancer, chemotherapy, Markov model

Key points

- Our study provided the first assessment of the cost-effectiveness of durvalumab plus chemotherapy for the first-line treatment of advanced biliary tract cancer and showed that the regimen was not cost-effective for both US and Chinese payers. Further price reductions for durvalumab were needed.

1. Introduction

Biliary tract cancers (BTCs) includes Intrahepatic, perihilar, distal cholangiocarcinoma (based on the anatomical location of the biliary tract) and gallbladder carcinoma (1). Perihilarcholangiocarcinoma (pCCA) accounts for the highest proportion (50–60%), followed by Intrahepatic carcinoma Cholangiocarcinoma (iCCA) (20–30%) (2). Cholangiocarcinomas (CCAs) occur in 2.8–3.3 per 100,000 Asians and Hispanics (3). The iCCA mortality rate rose from 2.15 per 100,000 in 2009 to 2.95 per 100,000 in 2018, with an annual increase of 3.5% (4). The incidence of BTC is strongly associated with hepatitis C in US and European populations, whereas hepatitis B is significantly associated with the incidence of iCCA in Chinese and Korean populations (5, 6). In Asian countries, hepatolithiasis and gallbladder stones are risk factors for the high incidence of BTC, especially iCCA, and 70% to 90% of gallbladder cancer patients are secondary to chronic cholecystitis caused by stones (7). In addition, hepatobiliary fluke infection, primary sclerosing cholangitis, chronic inflammation with liver injury are also pathogenic factors (8–10). Cholangiocarcinoma has a poor prognosis, with a 5-year survival rate of about 10% (2). 75% of CCA patients are advanced at the time of diagnosis, and 70% of patients have disease recurrence after surgery, although surgery is the main treatment (11, 12). Chemotherapy is still the first-line treatment for advanced BTC. Since 2010, the ABC-02 trial in the United Kingdom established cisplatin plus gemcitabine (GP) as the first-line chemotherapy for advanced CCA. In this trial of 410 patients, gemcitabine plus cisplatin compared with gemcitabine alone, Improved median progression free survival (mPFS) (8.0 vs. 5.0 months) and median overall survival (mOS;11.7 vs. 8.1 months). Immune checkpoint proteins, which regulate the immune system, have the ability to recognize and destroy tumor cells. Among them, the immune checkpoint inhibitors (ICIs), including programmed cell death protein-1 (PD-1), programmed apoptosis ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), inhibit antitumor immune responses in solid tumors (13, 14). BTC is a highly heterogeneous tumor caused by tumor gene mutations, which may be related to the expression of neoantigens (14). The biochemical environment of immunosuppression is generated by the tumor microenvironment (15, 16). BTC shows immunogenic characteristics in tumor microenvironment, and relevant studies have shown the clinical value of ICIs in BTC, such as durvalumab (17, 18). Durvalumab is a human IgG1 monoclonal antibody that selectively binds PD-L1 (18). Durvalumab previously showed promising efficacy in a phase 2 trial of the combination of gemcitabine and cisplatin, with an objective response rate of 72%, and its randomized, double-blind, phase 3 trial (TOPAZ-1; Clinicialtrials.gov number, NCT03875235), durvalumab plus chemotherapy significantly improved OS (24.9 vs. 10.4%) and objective response rate (26.7 vs. 18.7%) (17).

Despite the promising clinical applications of these two treatments, their high cost had attracted great attention. According to previous studies, the cost-effectiveness analysis of durvalumab was mostly performed in patients with small-cell lung cancer and non-small-cell lung cancer (19, 20). Studies of PD-1 inhibitors in BTCs were lacking. Therefore, in this study, we aimed to compare the cost-effectiveness of durvalumab combined with GP in advanced BTC from the perspective of healthcare payers in China and the United States (US).

2. Methods

2.1. Population

The basic medical data used in this economic evaluation referred to a double-blind, placebo-controlled, phase 3 global study (TOPAZ-1). The recruited patients were those with previously untreated disease that was unresectable or metastatic at initial diagnosis as well as those who developed recurrent disease more than 6 months after surgery with curative intent and more than 6 months after the completion of adjuvant therapy. This study included 424 patients and included the experimental group (198 patients) that has received durvalumab therapy and a control group (226 patients) that has received GP monotherapy.

2.2. The model's structure

Our analysis included 424 patients who have enrolled in the TOPAZ-1 trial as the target population. Based on the TOPAZ-1 trial, the Markov model was constructed for cost-effectiveness analysis of durvalumab as the first-line treatment for patients with BTCs. The model was built and run using Treeage Pro 2021 (Inc, Williamstown, MA, USA). This model has often been used by researchers for pharmacoeconomic analyses of advanced and metastatic cancer treatment (21, 22). The model included three health states: PFS, progressive disease (PD) and death. In the initial stage of the model, all patients are in an PFS state. As the treatment progressed, the patient either moved to another state or stays in this state. When the disease progressed, we assumed that the patients received chemotherapy (FOLFOX), immunotherapy (durvalumab), anti-angiogenesis inhibitor (regorafenib),Other therapy (Irinotecan plus capecitabine) as standard second-line treatment, as recommended by the Chinese Society of Clinical Oncology (CSCO) guidelines (version 2022) and National Comprehensive Cancer Network (NCCN) Guidelines for the diagnosis and treatment of primary BTCs (version 2022.2) (23). Notably, once a patient entered the PD state, they cannot return to the SD state; they either remained in the PD state or were transferred to the death state during the subsequent cycle. The specific transitions of each state in the model were shown in Supplementary Figure 1.

In the TOPAZ-1 clinical trial, the mOS in the experimental group was 12.8 months compared to 11.5 months in the control group, for a total study duration of no more than 2 years. However, Immunotherapy had a delayed effect and may continue to exert its beneficial effects beyond the treatment period; therefore, it should be analyzed using from long-term data to avoid inaccuracies and uncertainties in the results. Hence, with reference to the dosing cycle of the TOPAZ-1 clinical trial, we set the cycle of the Markov model to 21 days and the time horizon of 10 years to simulate the entire life course of the patient (24). Study endpoints included total cost, life years (LYs), quality-adjusted life years (QALYs) and incremental cost effectiveness ratios (ICERs). A half-circle correction was conducted to simulate the transfer process more accurately. This research was based on the perspective of Chinese and US payers, applying discount rates of 3% and 5% to costs and utilities, respectively (25). For US payers, we set the willing to pay (WTP) threshold to $150,000/QALY. For Chinese payers, according to the World Health Organization (WHO), ICER was acceptable if

it was below three times the gross domestic product (GDP) per capita. We set the WTP threshold at three 3 times China's GDP per capita in 2021 (US $38334). The research methods followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Supplementary Table 1) (26).

2.3. Clinical data input

The survival data of the experimental and control groups were presented using the Kaplan–Meier (KM) curve of the TOPAZ-1 clinical trial. The GetData Graph Digitizer (version 2.26; http://getdata-graph-digitizer.com/download.php) was used to extract the data points on the KM curve. R software was used to run the algorithm of Guyot et al. to reconstruct the extracted curve (27). We selected the best distribution from the exponential, weibull, gamma, log-normal, log-logistic and gompertz distributions to fit the reconstructed individual patient data (28). According to the Akaike Information Criterion (AIC) and Bayesian information Criterion (BIC), log-logistic and gamma distributions were selected to predict the long-term survival status of patients (Supplementary Figure 2). Ishak et al. have reported that in the process of fitting the parameter distribution to the survival model, lower AIC and BIC values provide objective criteria for the final selection of the distribution (29). The selection process for the distribution and goodness of fit is shown in Supplementary Table 2. The transition probability between the states of the Markov model was calculated using the method described by Liu et al. (30). This method reasonably corrects the time-dependent transition probability of a dynamic Markov model.

2.4. The utility and cost estimates

We were unable to obtain specific utility values for the patients with PFS and PD status. We used data from previously published studies as the health utility of BTCs patients in PFS and PD states (0.76 for PFS and 0.68 for PD) (31). To simplify the calculation, Grade 3 or higher adverse events (≥3 AEs) with the highest incidence difference between the durvalumab plus GP and GP groups were selected. Costs were converted based on 2021 US dollar exchange rates (USD 1.0 = CNY 6.34). We only consider the direct costs associated with medication, follow-up treatment, administration, laboratory tests and major ≥3 AEs according to the TOPAZ-1 trial. We obtained the latest prices of the drugs involved in the study through the sales prices of local hospitals or by consulting local drug suppliers. The upper and lower price limits of the drugs were determined by referring to all winning bids on the national pharmaceutical data platform (www.yaozh.com). For advanced BTCs, according to China's National Basic Medical Insurance, Industrial injury insurance and maternity insurance drug catalog (32), durvalumab could not be covered to partially reduce patient payments. We present the prices of the relevant drugs as costs both before and after health insurance coverage in Table 1. Except for the cost of ≥3 AEs as a one-time cost input model, the costs were calculated based on the dose used in the clinical trial and on a three-week cycle. As some of the costs referred to previously published literature, we used the consumer price index (CPI) inflation calculator to adjust these costs to 2022 prices (38).

The drug dose was based on actual clinical trials. In the GP plus durvalumab group, the patients received 1,500 mg of durvalumab and gemcitabine (1,000 mg/m^2) and cisplatin (25 mg/m^2) once every 3 weeks. In the control group, the patients received gemcitabine (1,000 mg/m^2) and cisplatin (25 mg/m^2) once every 3 weeks. According to a report on the status of Chinese residents' nutrition and chronic diseases in 2020, the average weight of the adult Chinese population was 64.8 kg (39). However, considering the long progression of BTCs, most patients are likely to be middle-aged and older adults, and in the advanced stage of the disease, patients are likely to suffer from weight loss and other discomforts. Therefore, we assumed that the average weight of patients was 60 kg. The weight set would be used to calculate the drug dose per cycle for durvalumab. A total of 42.5% of patients in the durvalumab plus GP group and 49.4% in the GP group received subsequent treatments.

2.5. Sensitivity analyses

A one-way sensitivity analysis was carried out to explore the parameters that might affect the ICER and the extent to which they might do so. Each parameter was independently changed by assuming ±20% of the expected value to determine the obvious influence on decision-making. In the probabilistic sensitivity analysis (PSA), we chose appropriate distributions for the parameters relevant to the inclusion in the model, e.g., costs (adverse effects of drugs and treatments) were gamma and risks (AEs) and health utility scores (PFS, PD and AE) were beta distributions. All parameters fluctuated between the 95% confidence interval (CI) (40).

3. Results

3.1. Base-case analysis

Our model simulated the cost effectiveness of durvalumab or placebo combined with chemotherapy for 10 years in patients with advanced BTC. The results of the Base-Case Analysis were presented in Table 2. From the perspective of the US payers, the total cost incurred in the chemotherapy group was $56,157.05, with a health output of 1.10 QALYs and 1.66 LYs. The total cost incurred in the durvalumab plus chemotherapy group was $217,069.25 with a health output of 1.52 QALYs and 2.30 Lys (Figure 1). Therefore durvalumab plus chemotherapy incurred additional costs of $160,912.20 and 0.42 QALYs, resulting in ICERs of $381,864.39/QALY. From the perspective of the Chinese payers, compared to the chemotherapy group, the durvalumab plus chemotherapy group incurred an additional cost of $154,904.98, resulting in an ICER of 367,608.51 /QALY (Figure 2).

3.2. Sensitivity analyses

The results of the deterministic sensitivity analysis were shown in the tornado diagram (Figures 3, 4). The main parameters that influenced the results of the analysis included the cost of durvalumab, the utility of PD and PFS status, with other parameters having minimal impact on the results. From the perspective of the US payers, when the price of durvalumab was varied at the

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TABLE 1 Basic parameters input to the model and the ranges of the sensitivity analyses.

Variable	Baseline value	Range		Distribution	References
		Minimum	Maximum		
Log-logistic OS survival model in durvalumab + chemotherapy group	Shape = 1.81; Scale = 13.55	Fixed in model		ND	Model fitting
Log-logistic OS survival model in chemotherapy group	Scale = 2.22; Scale = 11.68	Fixed in model		ND	Model fitting
Log-logistic PFS survival model in durvalumab + chemotherapy group	Scale = 2.19; Scale = 7.07	Fixed in model		ND	Model fitting
Gamma PFS survival model in chemotherapy group	Scale = 2.76; rate = 0.38	Fixed in model		ND	Model fitting
Risk for main adverse events					
Durvalumab + chemotherapy					
Neutrophil count decreased	0.207	0.1656	0.2484	Beta	(17)
Neutropenia	0.192	0.1536	0.2304	Beta	(17)
Anemia	0.189	0.1512	0.2268	Beta	(17)
Platelet count decreased	0.08	0.064	0.096	Beta	(17)
Chemotherapy					(17)
Neutrophil count decreased	0.254	0.2032	0.3048	Beta	(17)
Neutropenia	0.202	0.1616	0.2424	Beta	(17)
Anemia	0.187	0.1496	0.2244	Beta	(17)
Platelet count decreased	0.076	0.0608	0.0912	Beta	(17)
Health utility scores					
Utility of PFS	0.76	0.61	0.91	Beta	(33)
Utility of PD	0.68	0.54	0.82	Beta	(33)
Drug costs in the US, $/per cycle					
Gemcitabine	15.06	12.04	18.07	Gamma	CMS
Cisplatin	8.72	6.97	10.46	Gamma	CMS
Durvalumab	11,730	9,384	14,076	Gamma	CMS
Oxaliplatin	26.76	21.41	32.11	Gamma	CMS
Calcium Folinate (CF)	52.48	41.98	62.97	Gamma	CMS
Fluorouracil	18.57	14.86	22.29	Gamma	CMS
Irinotecan	35.88	28.70	43.05	Gamma	CMS
Capecitabine	180.6	144.48	216.72	Gamma	CMS
Regorafenib	21,546	17,236.8	25,855.2	Gamma	CMS
Drug costs in China, $/per cycle					
Gemcitabine	5.92	4.74	7.11	Gamma	b
Cisplatin	4.96	3.96	5.95	Gamma	b
Durvalumab	11,225.18	8,980.15	13,470.22	Gamma	b
Oxaliplatin	112.14	89.71	134.57	Gamma	b
Calcium Folinate (CF)	22.24	17.79	26.69	Gamma	b
Fluorouracil	140.97	112.77	169.16	Gamma	b
Irinotecan	547.28	437.83	656.74	Gamma	b
Capecitabine	43.2	11.94	99.73	Gamma	b

(Continued)

TABLE 1 (Continued)

Variable	Baseline value	Range		Distribution	References
		Minimum	Maximum		
Regorafenib	1,495.21	1,196.17	1,794.25	Gamma	b
Laboratory_test/per cycle-First hospitalization	482.07	45.60	662.13	Gamma	b
Laboratory_test in PFS status	266.00	91.96	446.06	Gamma	a
Laboratory_test in PD status	390.57	142.19	626.12	Gamma	a
Imaging examination in first hospitalization	1,457.11	1,221.95	1,832.77	Gamma	a
Imaging examination in PFS status	246.91	11.75	622.57	Gamma	a
Imaging examination in PD status	466.62	246.83	1,832.77	Gamma	a
Bed fees	349.12	49.46	1,219.47	Gamma	a
Care costs	404.74	71.10	1,030.49	Gamma	a
Expenditures on main AEs, $					
Neutrophil count decreased	466	373	559	Gamma	(34)
Anemia	531	425	638	Gamma	(34)
Neutropenia	354	283	425	Gamma	(34)
Platelet count decreased	1,814	1,451	2,177	Gamma	(35)
Disutility due to AEs					
Leukopenia	−0.09	−0.072	−0.108	Beta	(36)
Anemia	−0.125	−0.100	−0.150	Beta	(36)
Neutropenia	−0.09	−0.072	−0.108	Beta	(36)
Thrombocytopenia	−0.20	−0.160	−0.240	Beta	(37)
Risk for subsequent therapy					
Durvalumab + chemotherapy					
Chemotherapy	0.417	0.334	0.500	Beta	(17)
Targeted Therapy	0.035	0.028	0.042	Beta	(17)
Immunotherapy	0.009	0.007	0.011	Beta	(17)
Other	0.044	0.035	0.053	Beta	(17)
Chemotherapy					(17)
Chemotherapy	0.479	0.383	0.575	Beta	(17)
Targeted Therapy	0.047	0.038	0.056	Beta	(17)
Immunotherapy	0.047	0.038	0.056	Beta	(17)
Other	0.081	0.065	0.097	Beta	(17)

[a]Based on real hospital data.
[b]Comprehensive pricing and range in conjunction with local hospital and Chinese pharmaceutical databases (https://www.yaozh.com).
CMS, Centers for Medicare & Medicaid Services (https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/2022-asp-drug-pricing-file) 2022 ASP Drug Pricing Files.
PD-L1, Programmed cell death-Ligand 1; AEs, Adverse events; OS, Overall survival; PFS, Progression-free survival.

given upper and lower limits, the ICER ranged from $311,653.61-$4452,075.17/QALY. However this was still well above the WTP threshold we set ($15,000/QALY). When the price of durvalumab was reduced by 67.4%, the ICER equaled $150,000/QALY. When the price of durvalumab was further reduced by 80.9%, the ICER equaled $100,000/QALY. The results of the PSA analysis showed a 0% probability of durvalumab plus chemotherapy regimens being cost effective at a WTP threshold of $150,000/QALY in the cost effectiveness acceptable curves (Figures 5, 6). Incremental cost scatter plots showed that the results of all Monte Carlo simulations were distributed above the WTP line, so that durvalumab plus chemotherapy was not cost-effective when all parameters vary within a given range. For Chinese payers, since the WTP thresholds in China was much lower than in the US, all parameters were equally not cost effective in the range of variation.

4. Discussion

Locally advanced BTC is too large and invasive of blood vessels to be surgically resected, and in the last decade, gemcitabine combined with cisplatin has usually been the first-line treatment option for

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TABLE 2 Base-case analysis results.

Strategies	Cost	Incr Cost	LYs	Incr LYs	ICER/ LYs	QALYs	Incr QALYs	ICER/QALYs
US payer perspective								
Chemotherapy	56,157.05		1.66			1.10		
Durvalumab plus chemotherapy	217,069.25	160,912.20	2.30	0.64	251,818.78	1.52	0.42	381,864.39
Chinese payer perspective								
Chemotherapy	49,218.34		1.66			1.10		
Durvalumab plus chemotherapy	204,123.32	154,904.98	2.30	0.64	242,417.81	1.52	0.42	367,608.51

Incr Cost, Incremental cost; LYs, life-years; Incr LYs, Incremental life-years; QALYs, Quality-adjusted life-years; Incr QALYs, Incremental *Quality*-adjusted life-years.

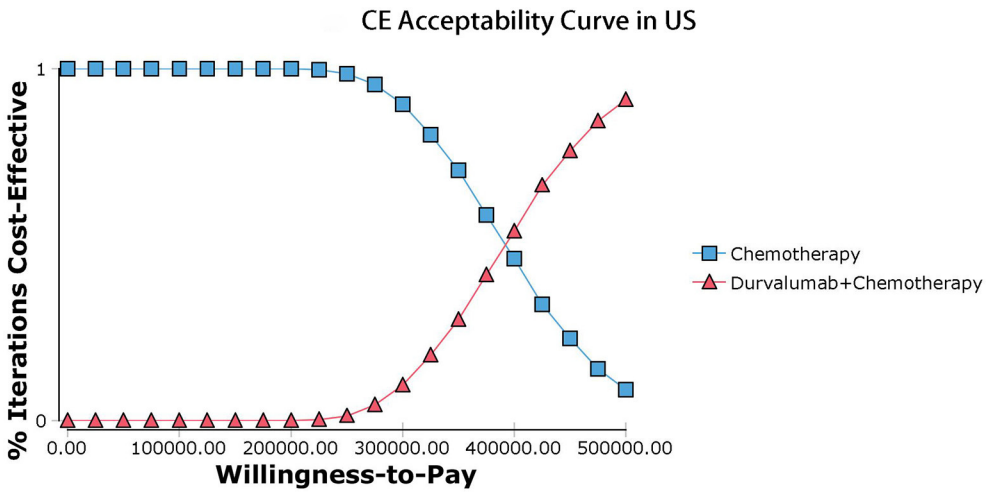

FIGURE 1
Acceptability curves in US.

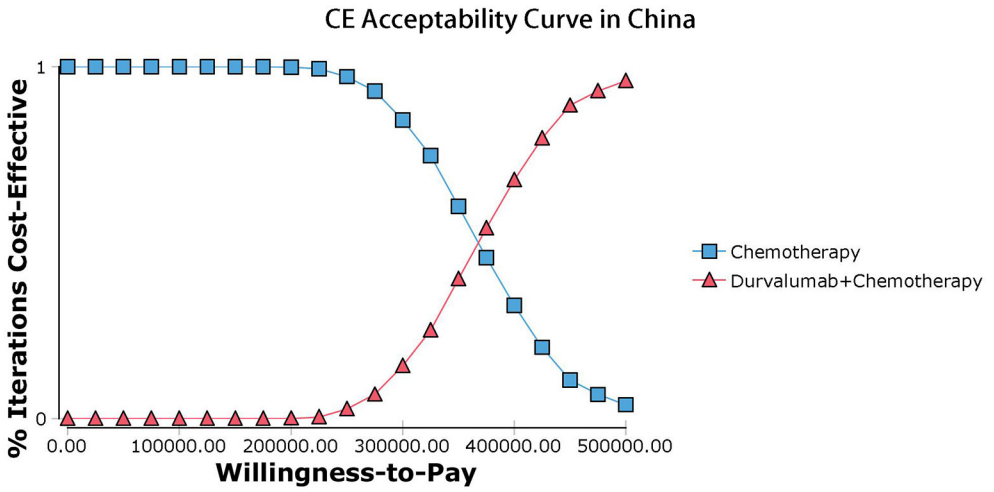

FIGURE 2
Acceptability curves in China.

such patients. However, chemotherapy alone has been ineffective, with limited patient benefit and a median OS of only 11.7 months (41). More recently, the TOPAZ-1 trial reported exciting clinical results with durvalumab in combination with chemotherapy for bile duct cancer. Durvalumab in combination with chemotherapy significantly improved OS and PFS in patients with BTC compared to standard chemotherapy, marking a milestone breakthrough in the treatment of BTC. The marketing application for a new indication for durvalumab in combination with chemotherapy for the first-line treatment of BTC has now been accepted by the Food and Drug

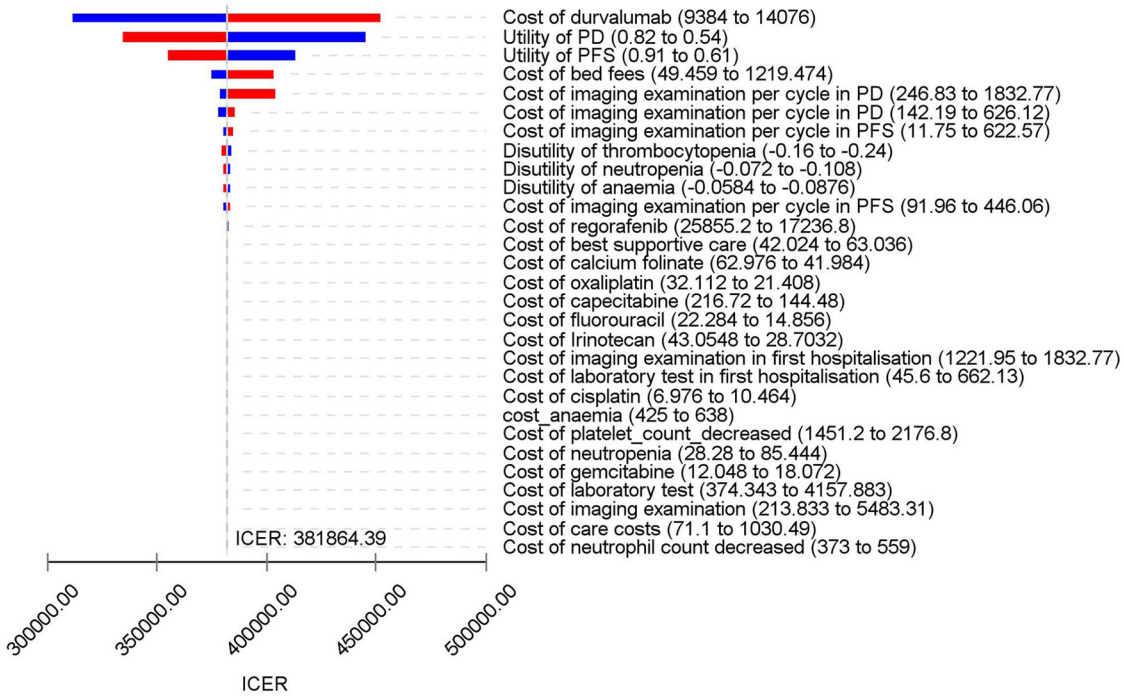

FIGURE 3
Tornado diagram for one-way sensitivity analysis in US.

Administration (FDA) and granted priority review. However, before clinicians can formally use this immune-combination chemotherapy regimen in clinical practice for patients with BTC, there are still some questions to be explored. As the most costly disease to treat in the United States, the cost of cancer treatment has increased significantly over the past decade and is still on an upward trend. The financial toxicity of ICI combination chemotherapy regimens, while improving efficacy, is seen as a negative consequence for cancer survivors (42). Excluding hospitalization expenses and toxicity, the direct cost of immunotherapy has exceeded the income of middle-class American families, and more than 1 in 3 patients cannot afford the financial toxicity of ICI, resulting in poorer quality of life and lower survival rates (43). Clinicians need to weigh the dual benefits of treatment cost and efficacy to develop the best treatment plan for patients of different economic levels. Therefore, to better facilitate the use of durvalumab in combination with chemotherapy regimens for bile duct cancer in clinical practice, it is necessary to evaluate its economics in terms of both cost and efficacy.

There was no study evaluating the economics of durvalumab in the treatment of BTC. Based on the latest clinical evidence from the TOPAZ-1 trial, our study constructed a Markov model to evaluate the cost-effectiveness of durvalumab combined with chemotherapy in the first-line treatment of BTC. The results of our analysis showed that the ICERs for durvalumab in combination with chemotherapy in the US and China were $426,301.52/QALY and $410,227.52/QALY, respectively. For US and Chinese payers, durvalumab plus chemotherapy did not offer a cost-effective advantage. The results of the sensitivity analysis showed that the price of durvalumab was a factor sensitive to the results of the analysis, followed by the utility of PD and PFS status. However, ICER far exceeds the WTP for US payers. All analyses showed no cost-effectiveness when all parameters were varied within a given interval. At current prices, the combination of durvalumab with chemotherapy for BTC is not economically advantageous, so further reductions in the cost of durvalumab are necessary. Further analysis of the price of durvalumab showed that durvalumab in combination with chemotherapy was only cost-effective when the price of durvalumab fell by 67.4% or more. If the WTP threshold of $100,000/QALY is used, the price of durvalumab needs to be reduced by more than 80.9%.

As the efficacy of durvalumab in combination with chemotherapy for the first-line treatment of BTC has only recently been revealed, there are still no studies evaluating the cost-effectiveness of this treatment option. Based on the current widespread use of durvalumab in lung cancer immunotherapy, several studies had evaluated the cost effectiveness of durvalumab for the treatment of lung cancer. Zhang et al. evaluated the cost effectiveness of durvalumab in combination with chemotherapy for the first-line treatment of small cell lung cancer from a US payer perspective (44). Zhang's analysis showed that the ICER of durvalumab plus chemotherapy was $355,448.86/QALY compared to the platinum-based chemotherapy regimen plus etoposide, so the regimen was not cost-effective. This result was consistent with

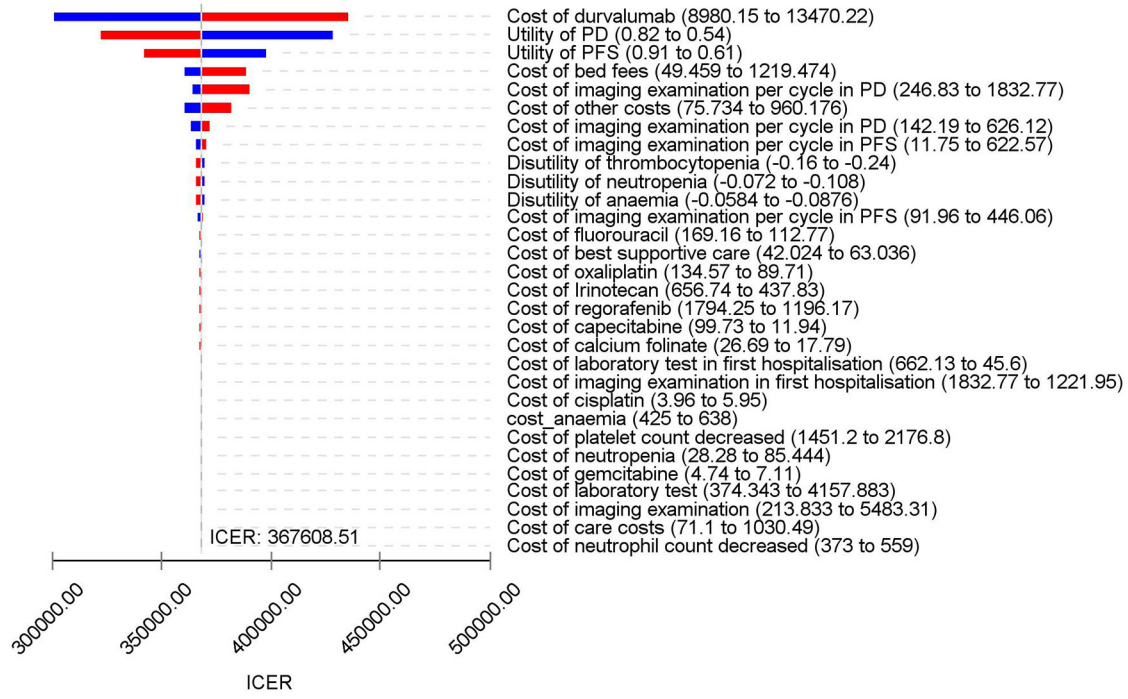

FIGURE 4
Tornado diagram for one-way sensitivity analysis in China.

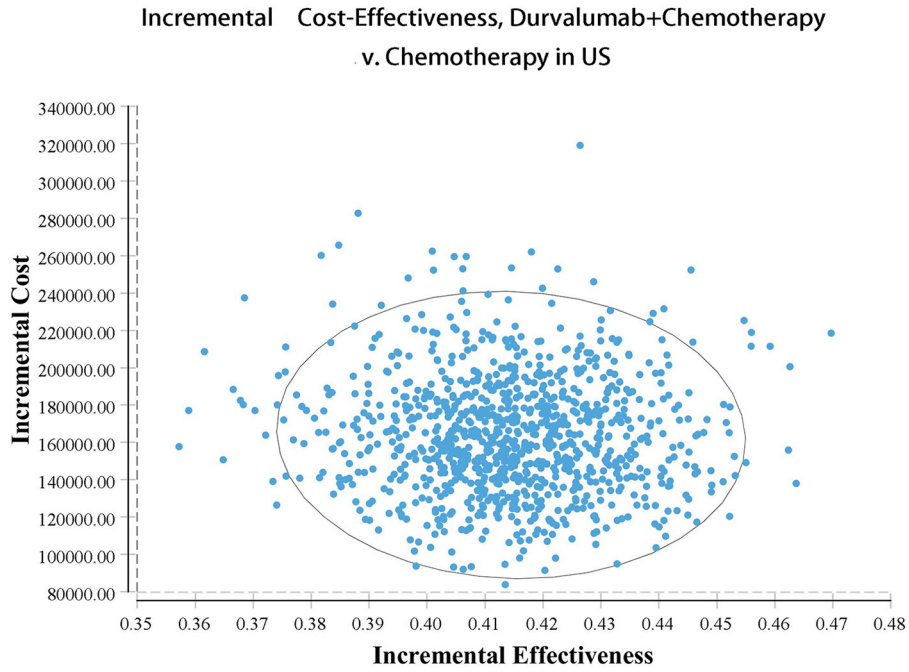

FIGURE 5
Incremental cost-effectiveness scatterplots in US.

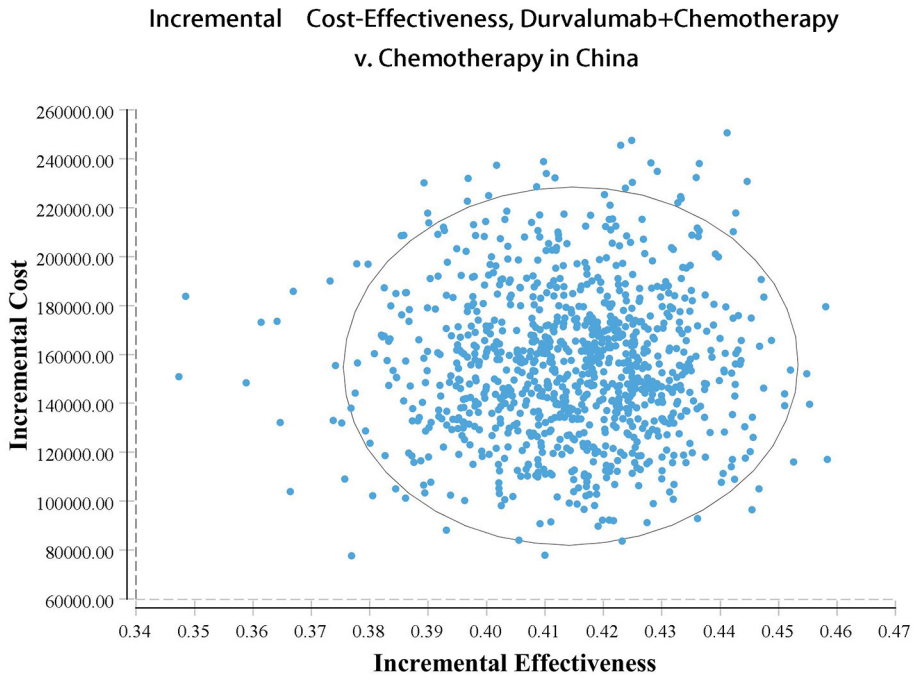

FIGURE 6
Incremental cost-effectiveness scatterplots in China.

the findings of Lin et al. although the ICER for durvalumab in combination with chemotherapy in Lin et al.'s analysis was $216,953/QALY (45). In addition, durvalumab in combination with chemotherapy was also not cost-effective for Chinese payers (46). It can therefore be seen that the cost of durvalumab in combination with chemotherapy needs to be further reduced for first-line treatment of small cell lung cancer. In the case of consolidation therapy after radiotherapy for non-small cell lung cancer, Han et al. showed that durvalumab was cost effective for US payers (47). The affordability of durvalumab was further validated in a microsimulation model of 2 million simulated patients conducted by Criss et al. (48) and could be extended to applicability to the US health care system. A study from Italy and others showed that the ICER of durvalumab in consolidation therapy after radiotherapy for non-small cell lung cancer exceeded the WTP threshold and that the official price of durvalumab needed to impose a discount (above 13%) to be cost-effective (49). These findings suggested that durvalumab plus chemotherapy for consolidation after radiotherapy for non-small cell lung cancer may be cost-effective in China and US, but not in Italy and other countries, and therefore geographical differences should be fully taken into account when conducting cost-effectiveness analyses. In addition, the current studies have reported no cost-effectiveness when this regimen was used as first-line treatment for small cell lung cancer. And this conclusion was also applicable to the first-line treatment of patients with BTC. Our study validated this in the first-line treatment of BTC, where durvalumab in combination with chemotherapy was not cost-effective in China and US. Two articles about cost-effectiveness analysis of BTC, but both of them were the comparison between chemotherapy regimen (Gemcitabine plus Cisplatin vs. Gemcitabine Alone). In Roth's study (50), gemcitabine monotherapy had the highest probability of being cost-effective until a willingness-to-pay of $60,000, Cost-effective until a willingness-to-pay of $60,000,after which the GP strategy had the highest probability. However, Tsukiyama's study (51) showed that combination therapy is less cost-effective than monotherapy for treating advanced BTC in Japan. In our study, compared with GP scheme, durvalumab+GP has better effect, but due to the high price of durvalumab, durvalumab+GP scheme is not cost-effective compared with GP scheme regardless of willingness to pay in China and USA.When the price of durvalumab is reduced, we can expect that durvalumab combined with GP regimen will be more suitable as a preferred option for patients with advanced BTC.

This study has a number of limitations. First, our model simulates patients from the TOPAZ-1 trial, which only published follow-up data for durvalumab combined with chemotherapy for about 2 years, and we digitally extracted OS and PFS data for durvalumab combined with chemotherapy and estimated them by parameter-specific survival distributions. Despite having a good good goodness of fit, its true long-term efficacy remains uncertain, which is subject to further refinement by subsequent follow-up data. Second, given that few studies have reported health utility in patients with BTC and that no specific utility data have been published from the TOPAZ-1 trial, we must make assumptions about health utility. We refer to previous studies reporting health utilities for patients with liver cancer and assume that the utilities for patients with BTC are consistent with them. This could lead to potential bias in the results of the analysis. The results of the analysis remain robust over the range of variation in utility. Thirdly, we only considered the impact of ≥3 AEs (increased costs and loss of utility), with 1–2 AEs being ignored, which are usually not or rarely intervened in clinical practice. In addition, ≥3 AEs with an incidence of <5% were excluded from consideration,

although sensitivity analyses showed that AEs had only a limited impact on the results of the analysis.

5. Conclusions

In comparison to chemotherapy, durvalumab plus chemotherapy is not considered cost-effective for first-line treatment of advanced BTC, either in China or in the United States. Further price reduction of durvalumab is necessary.

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

Z-mY and ZX had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, concept and design, acquisition, analysis, or interpretation of data, drafting of the manuscript, and statistical analysis. HL and QL contributed to the critical revision of the manuscript for important intellectual content, obtained funding, administrative, technical, or material support, and supervision. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1046424/full#supplementary-material

SUPPLEMENTARY TABLE 1
CHEERS checklist.

SUPPLEMENTARY TABLE 2
AIC and BIC scores of fitted distribution.

SUPPLEMENTARY FIGURE 1
Markov state transition probability diagram.

SUPPLEMENTARY FIGURE 2
Fitting of OS and PFS survival curves to different parameter survival distributions.

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Effectiveness and cost-effectiveness analysis of 11 treatment paths, seven first-line and three second-line treatments for Chinese patients with advanced wild-type squamous non-small cell lung cancer: A sequential model

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Background: A total of 11 treatment sequences for advanced wild-type squamous non-small cell lung cancer are recommended by Chinese Society of Clinical Oncology Guidelines, consisting of seven first-line and three second-line treatments. Five of these treatments were newly approved in China between 2021 and 2022. We evaluated the effectiveness and cost-effectiveness of these strategies from the Chinese healthcare system perspective.

Methods: Network meta-analysis with non-proportional hazards was used to calculate the relative efficacy between interventions. A sequential model was developed to estimate costs and quality-adjusted life years (QALY) for treatment sequences with first-line platinum- and paclitaxel-based chemotherapy (SC) with or without nedaplatin, tislelizumab, camrelizumab, sintilimab, sugemalimab or pembrolizumab, followed by second-line docetaxel, tislelizumab or nivolumab. SC and docetaxel were used as comparators for first-line and second-line treatments, respectively. QALY and incremental cost-effectiveness ratio (ICER) were used to evaluate effectiveness and cost-effectiveness, respectively. Cost-effective threshold was set as USD 19,091. Subgroup analysis was conducted to determine the best first-line and second-line therapy.

Results: Pembrolizumab + SC, followed by docetaxel (PED) was the most effective treatment sequence. QALYs for patients received SC, nedaplatin + SC, tislelizumab + SC, sintilimab + SC, camrelizumab + SC, sugemalimab + SC, pembrolizumab + SC followed by docetaxel were 0.866, 0.906, 1.179, 1.266, 1.179, 1.266, 1.603, 1.721, 1.807; QALYs for SC, nedaplatin + SC followed by tislelizumab were 1.283, 1.301; QALYs for SC, nedaplatin + SC followed by nivolumab were 1.353, 1.389. Camrelizumab + SC, followed by docetaxel (CAD) was the most cost-effective. Compared to SC with or without nedaplatin, tislelizumab, or sintilimab followed by docetaxel, ICERs of CAD were USD 12,276, 13,210, 6,974, 9,421/QALY, respectively. Compared with nedaplatin or SC followed by tislelizumab, the ICERs of CAD were USD 4,183, 2,804/QALY; CAD was dominant compared with nedaplatin or SC followed by nivolumab; The ICER of sugemalimab + SC followed

by docetaxel and PED were USD 522,023, 481,639/QALY compared with CAD. Pembrolizumab + SC and camrelizumab + SC were the most effective and cost-effective first-line options, respectively; tislelizumab was the most effective and cost-effective second-line therapy. Tislelizumab used in second-line was more effective than first-line, no significant differences between their cost-effectiveness. Sensitivity and scenario analysis confirmed robustness of the results.

Conclusions: PED and CAD are the most effective and cost-effective treatment sequence, respectively; pembrolizumab + SC and camrelizumab + SC are the most effective and cost-effective first-line choice, respectively; tislelizumab is the most effective and cost-effective second-line choice.

KEYWORDS

advanced squamous non-small cell lung cancer, cost-effectiveness, treatment sequence, sequential model, non-proportional hazard models

Highlights

- What is already known about the topic?

Non-small-cell lung cancer (NSCLC) poses a significant burden on patients and the healthcare system owing to decreased quality of life, substantial economic burden. A total of 11 treatment sequences for advanced wild-type squamous non-small cell lung cancer are recommended by Chinese Society of Clinical Oncology Guidelines, consisting of seven first-line and three second-line treatments, five of them were newly approved in Chinese between 2021 and 2022.

- What does the paper add to existing knowledge?

First-line camrelizumab plus carboplatin and paclitaxel, followed by second-line docetaxel is the optimal treatment sequence in cost-effectiveness, while pembrolizumab plus carboplatin and paclitaxel (SC), followed by second-line docetaxel is the optimal treatment sequence in effectiveness. Pembrolizumab plus SC (P + C) and camrelizumab plus SC (CA + C) are the most effective and cost-effective therapy among seven available first-line treatments, respectively (SC, nedaplatin, tislelizumab, camrelizumab, sintilimab, sugemalimab or pembrolizumab in combination with SC), tislelizumab is the best second-line choice compared to nivolumab and docetaxel both in effectiveness and cost-effectiveness.

- What insights does the paper provide for informing health care-related decision making?

We provided a novel mirco-simulation sequential model to determine the optimal therapeutic pathway as certain reference for future research. The current National Reimbursement Drug List (NRDL) negotiation attaches great importance to direct evidence between innovative treatments, traditional pharmacoeconomics research of innovative treatments vs. standard treatments may be no longer applicable. In the upcoming 2022 NRDL negotiation, our research will provide comprehensive evidence for drug access negotiation and price setting for the all first- or second-line treatments of sq-NSCLC.

Introduction

The International Agency for Research on Cancer (https://www.iarc.who.int/) reported that, ∼19.3 million new cancer cases and nearly 10 million cancer-related deaths occurred worldwide in 2020 (1). Lung cancer accounted for 11.4% of the new cancer cases, ranking second after breast cancer (11.7%), and 18% of new cancer-related deaths, ranking first among all cancers (1). Non-small cell lung cancer (NSCLC) accounted for 80–85% of all lung cancers (2, 3), and nearly one-third of patients with NSCLC are diagnosed with the squamous histological subtype (4). Treatment development for squamous NSCLC (sq-NSCLC) has been stagnated, owing to its unique histopathology and molecular characteristics (5).

Many chemotherapy drugs have been approved in China for treating sq-NSCLC, including cisplatin or carboplatin combined with gemcitabine, docetaxel, paclitaxel, or nedaplatin. Under chemotherapy treatment, patients with advanced sq-NSCLC have low survival rates, the median progression-free survival (PFS) of patients with stage IIIB–IV sq-NSCLC was ∼4–6 months (6–16), and the median overall survival (OS) was 10–15 months (7–17), Programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors are considered to be a breakthrough in the treatment of sq-NSCLC. PD-L1 is expressed in normal tissues but is overexpressed in various types of tumors. In NSCLC, PD-L1 expression levels were found to increase by 35–95% (18). Activation of immune cells increased the expression of the PD-1/PD-L1 immune checkpoint inhibitors and restored or even enhanced the ability of immune cells to kill tumor cells by blocking PD-1/PD-L1 expression (19). Many studies have shown that combining immunotherapy and chemotherapy can significantly improve PFS and OS in patients with stage IIIB–IV sq-NSCLC. Specifically, the median PFS was approximately 8–9 months, and the median OS was 15–18 months, both showed significant longer survival benefits than chemotherapy alone (10–15, 20). Many immune checkpoint inhibitors for treating advanced sq-NSCLC have been approved in China, including pembrolizumab, tislelizumab, camrelizumab, sintilimab, and sugemalimab, atezolizumab and nivolumab.

Although PD-1/PD-L1 inhibitors have improved outcomes in patients with metastatic diseases, they are also associated

with significant higher cost. In current healthcare environments, policy makers, clinicians, and patients will all benefit from a sound framework for determining the benefits of different therapeutic choices in oncology based on both effectiveness and cost-effectiveness. The current National Reimbursement Drug List (NRDL) negotiation attaches great importance to direct evidence between innovative treatments, traditional pharmacoeconomics research of innovative treatments vs. standard treatments may be no longer applicable.

For the treatment of wild-type advanced sq-NSCLC, seven first-line treatments and three second-line treatments were first-level recommended by Clinical Oncology Guidelines 2022 (CSCO 2022) (21). Increasing in treatment options makes it more difficult to choose an effective and cost-effective clinical treatment path for clinicians and patients. More importantly, health policy makers are facing great challenges in drugs market access, market pricing, and rational allocation of health resources. Direct evidence between innovative treatments is more important for NRDL negotiation, therefore, there is an urgent need to systematically compare the effectiveness and cost-effectiveness of these treatments or sequential pathways, so as to promote clinical rational drug use, scientific formulation of health policy and rational allocation of medical resources. Therefore, evidence of systematic evaluation of same-type therapies is urgently needed. Therefore, we mainly aimed to evaluate the effectiveness and cost-effectiveness of currently available first-line therapies, second-line therapies and treatment sequences recommended by CSCO 2022 for patients with wild-type advanced sq-NSCLC (21).

Materials and methods

Target population and treatment strategies

The target population was Chinese adults (aged ≥ 18 years) who had pathologically confirmed stage IIIB–IV wild-type sq-NSCLC with unlimited PD-L1 expression. The population received no previous systemic therapy. We modeled a hypothetical cohort with the same baseline characteristics as the patients enrolled in the original clinical trials. For dosage calculation, the body surface area and creatinine clearance rate were assumed as 1.72 m^2 and 70 ml/min (22). According to the CSCO 2022 (21), the first-level recommended first-line regimens for performance status (PS) 0–1 patients with advanced sq-NSCLC and unlimited PD-L1 expression include cisplatin or carboplatin combined with gemcitabine, docetaxel, or paclitaxel (standard chemotherapy), nedaplatin combined with docetaxel (N + C), paclitaxel and platinum combined with pembrolizumab (P + C), paclitaxel and platinum combined with tislelizumab (T + C), paclitaxel and platinum combined with camrelizumab (CA + C), platinum combined with gemcitabine and sintilimab (SI + C), paclitaxel and platinum combined with sugemalimab (SU + C). Among these seven first-line therapies, T + C, CA + C, SI + C, and SU + C were newly approved for sq-NSCLC since 2021 in China. Nivolumab, tislelizumab and docetaxel are first-level recommended second-line treatments options for these patients, and tislelizumab was newly approved in 2022 for second-line treatment of sq-NSCLC. Because of the possible resistance among PD-1/PD-L1 drugs, few clinical applications and evidence, we did not consider cases where immune checkpoint inhibitors were used in the first- and second-line treatments simultaneously. Therefore, we assessed 11 treatment strategies (see Figure 1): 1. first-line N + C followed by second-line docetaxel (ND); 2. first-line N + C followed by second-line tislelizumab (NT); 3. first-line N + C followed by second-line nivolumab (NN) (16); 4. first-line standard chemotherapy followed by second-line docetaxel (CD); 5. first-line standard chemotherapy followed by second-line tislelizumab (CT); 6. first-line standard chemotherapy followed by second-line nivolumab (CN) (10–13, 16, 20); 7. first-line P + C followed by second-line docetaxel (PED) (13); 8. first-line SI + C followed by second-line docetaxel (SID) (12); 9. first-line CA + C followed by second-line docetaxel (CAD) (11); 10. first-line T + C followed by second-line docetaxel (TID) (20); 11. first-line SU + C followed by second-line docetaxel (SUD) (10). According to randomized clinical trials (RCTs) (23, 24), clinical diagnosis, and treatment experience (25, 26), the PS of patients with advanced sq-NSCLC tends to be poor after two-line active treatments. Therefore, the best supportive treatment (BSC) accounts for the largest proportion of third-line treatment, surpassing sum of other active treatments' proportions. Thus, patients with disease progression after the first- and second-line treatments were assumed to receive the BSC in this model. Standard chemotherapy and docetaxel were used as comparators for first-line and second-line treatments, respectively. We explored the impact of uncertainty about the third-line treatment on the results by scenario analysis. Specific medication, dosages, treatment durations are provided in the Supplementary material 1.

Decision analytic model

We developed a sequential micro-simulation model in an academic medical setting with 21-day cycle length to compare different treatment strategies in the context of the Chinese healthcare system. The sequential model is a modification of the traditional partitioned survival model. In the traditional three-state partitioned survival model, post-progression treatment pathways are indistinguishable, and cycle costs for all PD stages can only be unique. However, for sq-NSCLC, the treatment of patients after progression follows certain treatment pathways, i.e., second-line treatment, then third-line... until finally they would receive best supportive care and end-of-life treatment. It is in this context that the sequential model is created, enabling accurate simulation of multiple lines of treatment pathways for patients, thereby improving the accuracy of cost and health. A cohort of 10,000 simulated patients with advanced sq-NSCLC experienced four states: PFS, first-stage progressed disease (PD), end-stage PD, and death. All the simulated patients began progression-free before receiving first-line therapies, and those with PD were followed up through second-line treatment, third-line treatment, and death. Details of the model structure and treatment strategies are shown in Figure 1, modeling process and validation are provided in Supplementary material 2. Microsoft Excel 2019 was used for model building. The reporting of the economic evaluation followed the ISPOR guideline Consolidated Health

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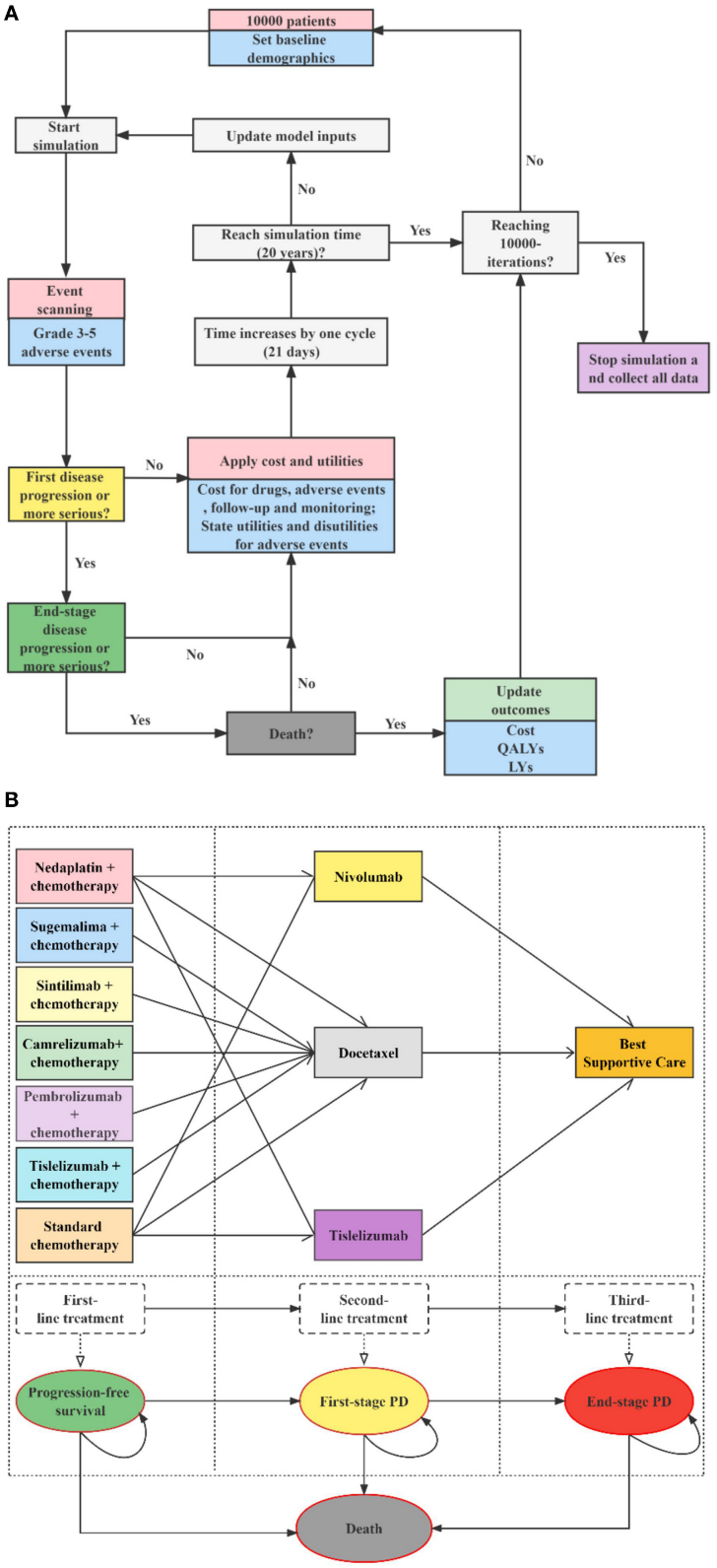

FIGURE 1
Decision analytic model and treatment strategies. **(A)** Microsimulation model structure (above), **(B)** Multi-state survival model for treatment strategies (below), PD, progressive disease; LYs, life-years; QALYs, quality-adjusted life years.

Economic Evaluation Reporting Standards (CHEERS) checklist (Supplementary material 4).

Sources of treatment efficacy

Relative efficacy of the different treatments compared to the reference treatments were assessed by network meta-analysis (NMA). Briefly, we systematically searched PubMed, Embase, ClinicalTrials.Gov, European Society for Medical Oncology, American Society of Clinical Oncology, and World Conference on Lung Cancer databases as of May 2022 (27–31). Bayesian parametric survival NMA was used to synthesize survival data from eligible trials. Details of the eligibility criteria, search strategies are provided in Supplementary material 2. We conducted three NMAs in our study. For the NMA of first-line PFS, we estimated the time-varying hazard ratios (HRs) between the combination therapies N + C, P + C, T + C, CA + C, SI + C or SU + C and standard chemotherapy. Then, the expected survival curves for the combination therapies were derived by applying the HRs to the Kaplan-Meier survival curves for standard chemotherapy (reference treatment). The reference PFS curve for the first-line was derived from the CameL-sq, in which the final rate of the PFS was 5% (11). For this analysis, in the platinum- and paclitaxel-based chemotherapy regimens, cisplatin and carboplatin, and paclitaxell, gemcitabine, and docetaxel were not differentiated because their prices were similarly low and their survival outcomes were almost the same, and these drugs were used in similar capacities in common clinical practice (6, 32, 33). Similar to the first-line NMA, for the second-line NMAs of PFS and OS, we estimated the HRs between nivolumab, tislelizumab and docetaxel. The referred PFS and OS curves were extracted from the docetaxel in Checkmate-078 China (final rates of PFS and OS were <3 and 5% for docetaxel) (23, 24). We also considered natural mortality after the plateau at the end of the survival curves, which were extracted from China's 6th National Census (34). The original PFS and OS curves used in this study are presented in Supplementary material 2.

Model transitions and survival estimates

We used GetData Graph Digitizer (v2.26, http://getdata.sourceforge.net/download.html) to extract survival data from published PFS and OS Kaplan-Meier curves. To reconstruct individual patient data, we used the Guyot's method, which is the most accurate data reproduction method currently known for cases where individual patient data are not available (35, 36). Log cumulative hazards and schoenfeld residual test plots (Supplementary material 2) showed proportional hazard (PH) or piecewise models were not suitable in this analysis. In accordance with the shapes of the survival curves, the non-PH NMA models considered in this study were first- and second-order fractional polynomial (FP) models (37). We fitted first- and second-order FP models with power parameters −2, −1, −0.5, 0, 0.5, 1, 2, and 3, with three parallel Markov chains consisting of 10,000 samples after a 10,000 samples burn-in. To reconstruct and extrapolate the PFS curve of the standard chemotherapy, and the OS and PFS curves of the second-line docetaxel, we considered parametric functions including Exponential, Weibull, Gompertz, Gamma, Log-logistic, Log-normal, Generalized Gamma, GenF, FP, Restricted Cubic Spline, and Royston and Parmar (RP) models. Goodness-of-fit was evaluated by visual inspection of survival curves, Akaike information criterion (AIC) and deviance information criterion (DIC). Lower AIC and DIC combined with reasonable visual effects indicated a better performance of the selected model (38). Survival modeling was conducted in R (v4.1.2) and Winbugs (v1.4.3) (39, 40). R codes for relative methods can be found on Github (https://github.com/TaihangShao/NMA_methodology).

Model validation

The face validity (model structure and assumption, data sources, and results) of the model was evaluated by clinical experts. Authors MZ and TS did the coding, and the results produced by the model were compared with previously reported results for cross-validation.

Costs

The costs of implementing each treatment were derived the perspective of Chinese healthcare system. All cost data were inflated to 2022, shown as 2022 US dollars (1 USD = 6.36 Chinese Yuan). We considered only direct medical costs, including drug costs, follow-up costs, monitoring costs, death costs, and costs for treatment of adverse reactions (AEs). Drug prices were obtained from the latest local public bid-winning price or public databases (41–43). The prices of camrelizumab used in first-line or tislelizumab used in second-line were assumed to be the same as other indications of them which have entered the NRDL, considering the newly approved indication of sq-NSCLC would likely to be included in the list and the price is the same for all indications of the same drug in the NRDL. Prices for paclitaxel and gemcitabine were from the fifth batch of bids for centralized drug procurement of drugs in China in 2021 (41–43). Because carboplatin, cisplatin, paclitaxel, docetaxel, and nedaplatin have multiple dosage forms in the Chinese market, we chose the commonly used dosage combination under the principle of minimizing cost. Follow-up costs and monitoring costs were derived from the healthcare documents (44), which included CT examination, blood test, urinalysis, and blood biochemical examination, as wells as diagnosis fee, injection fee, nursing fee, and bed fee. Costs of BSC and end-of-life were extracted from published literature. We considered only severe AEs (≥grade 3) with rates >5%. AE related treatment costs and durations of AE were extracted from published articles. All AEs were assumed to occur during the first cycle (45). Details are listed in Table 1.

Utilities

Health state utilities were sourced from published literature. For the base-case analysis, utilities were derived from the patient-level European Organization for Research and Treatment Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) scores in

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TABLE 1 Parameters used in the model.

Item	Mean (range)	Distribution	Sources
Clinical-related parameters			
First-order fractional polynomial model for first-line PFS curve: $p = -2$			
PFS_HR_Scale (N + C vs. Standard chemotherapy)	−0.016 (-0.499 ~ 0.467)	Lognormal	NMA
PFS_HR_Scale (SI + C vs. Standard chemotherapy)	−0.735 (-1.029 ~ 0.442)	Lognormal	NMA
PFS_HR_Scale (P + C vs. Standard chemotherapy)	−1.255 (-1.678 ~−0.832)	Lognormal	NMA
PFS_HR_Scale (T + C vs. Standard chemotherapy)	−0.589 (-0.99 ~−0.197)	Lognormal	NMA
PFS_HR_Scale (CA + C vs. Standard chemotherapy)	−1.095 (-1.368 ~−0.828)	Lognormal	NMA
PFS_HR_Scale (SU + C vs. Standard chemotherapy)	−1.191 (-1.58 ~−0.806)	Lognormal	NMA
PFS_HR_Shape (N + C vs. Standard chemotherapy)	−4.314 (-11.076 ~ 2.094)	Lognormal	NMA
PFS_HR_Shape (SI + C vs. Standard chemotherapy)	0.849 (-1.671 ~ 3.263)	Lognormal	NMA
PFS_HR_Shape (P + C vs. Standard chemotherapy)	0.934 (-2.192 ~ 3.717)	Lognormal	NMA
PFS_HR_Shape (T + C vs. Standard chemotherapy)	−0.404 (-3.068 ~ 1.877)	Lognormal	NMA
PFS_HR_Shape (CA + C vs. Standard chemotherapy)	1.022 (-0.826 ~ 2.792)	Lognormal	NMA
PFS_HR_Shape (SU + C vs. Standard chemotherapy)	1.548 (-0.655 ~ 4.071)	Lognormal	NMA
Second-order fractional polynomial model for first-line OS curve: p1 = −0.5, p2 = 0			
OS_HR_Scale (Nivolumab vs. Docetaxel)	2.231 (-3.239 ~ 7.493)	Lognormal	NMA
OS_HR_Scale (Tislelizumab vs. Docetaxel)	0.151 (-6.431 ~ 6.387)	Lognormal	NMA
OS_HR_Shape1 (Nivolumab vs. Docetaxel)	−3.328 (-9.684 ~ 3.238)	Lognormal	NMA
OS_HR_Shape1 (Tislelizumab vs. Docetaxel)	−0.786 (-8.365 ~ 7.201)	Lognormal	NMA
OS_HR_Shape2 (Nivolumab vs. Docetaxel)	−0.677 (-2.045 ~ 0.755)	Lognormal	NMA
OS_HR_Shape2 (Tislelizumab vs. Docetaxel)	0.187 (-1.822 ~ 1.54)	Lognormal	NMA
Second-order fractional polynomial model for first-line PFS curve: $p = -2$			
PFS_HR_Scale (Nivolumab vs. Docetaxel)	−0.891 (-1.263 ~−0.511)	Lognormal	NMA
PFS_HR_Scale (Tislelizumab vs. Docetaxel)	−1.059 (-1.347 ~−0.763)	Lognormal	NMA
PFS_HR_Shape (Nivolumab vs. Docetaxel)	0.675 (-0.253 ~−1.641)	Lognormal	NMA
PFS_HR_Shape (Tislelizumab vs. Docetaxel)	0.449 (-0.483 ~ 1.39)	Lognormal	NMA
Parametric model fit to the referred PFS and OS curves			
Log-logistic model for the first-line PFS curve (scale)	0.38	Constant	Parametric model
Log-logistic model for the first-line PFS curve (shape)	2.506	Constant	Parametric model
Exponential model for the second-line OS curve (scale)	1.043	Constant	Parametric model
Restricted cubic spline model for the second-line PFS curve (Gamma 0)	0.463	Constant	Parametric model
Restricted cubic spline model for the second-line PFS curve (Gamma 1)	0.305	Constant	Parametric model
Restricted cubic spline model for the second-line PFS curve (Gamma 2)	1.793	Constant	Parametric model
Restricted cubic spline model for the second-line PFS curve (Gamma 3)	0.114	Constant	Parametric model
Risk of grade 3–5 adverse events			
Neutropenia (P + C)	0.615 (0.492 ~ 0.738)	Beta	(13)
Neutropenia (SI + C)	0.486 (0.389 ~ 0.583)	Beta	(12)
Neutropenia (T + C)	0.517 (0.413 ~ 0.620)	Beta	(20)

(Continued)

TABLE 1 (Continued)

Item	Mean (range)	Distribution	Sources
Neutropenia (CA + C)	0.554 (0.444 ~ 0.665)	Beta	(11)
Neutropenia (N + C)	0.270 (0.216 ~ 0.323)	Beta	(16)
Neutropenia (Standard chemotherapy)†	0.488 (0.391 ~ 0.586)	Beta	(10–13, 16, 20)
Neutropenia (Docetaxel)	0.590 (0.472 ~ 0.708)	Beta	(46)
Neutropenia (SU + C)	0.325 (0.26 ~ 0.39)	Beta	(10)
Decreased platelet count (P + C)	0.077 (0.062 ~ 0.092)	Beta	(13)
Decreased platelet count (SI + C)	0.453 (0.362 ~ 0.543)	Beta	(12)
Decreased platelet count (T + C)	0.058 (0.047 ~ 0.07)	Beta	(20)
Decreased platelet count (CA + C)	0.067 (0.054 ~ 0.081)	Beta	(11)
Decreased platelet count (Standard chemotherapy)†	0.171 (0.136 ~ 0.205)	Beta	(10–13, 16, 20)
Decreased platelet count (SU + C)	0.103 (0.083 ~ 0.124)	Beta	(10)
Anemia (SU + C)	0.134 (0.108 ~ 0.161)	Beta	(10)
Anemia (SI + C)	0.335 (0.268 ~ 0.402)	Beta	(12)
Anemia (T + C)	0.075 (0.06 ~ 0.09)	Beta	(20)
Anemia (CA + C)	0.104 (0.083 ~ 0.124)	Beta	(11)
Anemia (Standard chemotherapy)†	0.143 (0.115 ~ 0.172)	Beta	(10–13, 16, 20)
Leukopenia (P + C)	0.354 (0.283 ~ 0.425)	Beta	(13)
Leukopenia (SI + C)	0.363 (0.291 ~ 0.436)	Beta	(12)
Leukopenia (Standard chemotherapy)†	0.284 (0.227 ~ 0.341)	Beta	(10–13, 16, 20)
Leukopenia (T + C)	0.225 (0.18 ~ 0.27)	Beta	(20)
Leukopenia (CA + C)	0.301 (0.24 ~ 0.361)	Beta	(11)
Leukopenia (N + C)	0.177 (0.142 ~ 0.233)	Beta	(16)
Leukopenia (SU + C)	0.141 (0.113 ~ 0.169)	Beta	(10)
Leukopenia (Docetaxel)‡	0.342 (0.274 ~ 0.41)	Beta	(46)
Pneumonia (SI + C)	0.14(0.112 ~168)	Beta	(12)
Pneumonia (Standard chemotherapy)†	0.094 (0.076 ~ 0.113)	Beta	(10–13, 16, 20)
Pneumonia (Tislelizumab)	0.089 (0.071 ~ 0.107)	Beta	(46)
Hyponatremia (SI + C)	0.061 (0.049 ~ 0.074)	Beta	(12)
Hyponatremia (Standard chemotherapy)†	0.05 (0.04 ~ 0.06)	Beta	(10–13, 16, 20)
Asthenia (Docetaxel)‡	0.051 (0.041 ~ 0.062)	Beta	(46)
Time duration of grade 3–5 adverse events/days			
Neutropenia	6.4	Constant	(47)
Decreased platelet count	8.5	Constant	(47)
Anemia	51.2	Constant	(47)
Leukopenia	4.5	Constant	(47)
Pneumonia	10.0	Constant	(48)
Hyponatremia	8.0	Constant	(49)
Asthenia	7.0	Constant	Assumed
Cost-related parameters			
Cost of drugs/$			
Pembrolizumab/100 mg	2816.87 (1408.43 ~ 2816.87)	Gamma	(41, 43)

(Continued)

TABLE 1 (Continued)

Item	Mean (range)	Distribution	Sources
Camrelizumab/200 mg	460.31 (368.25 ~ 460.31)	Gamma	(41, 43)
Sintilimab/100 mg	169.79 (135.83 ~ 169.79)	Gamma	(41, 43)
Tislelizumab/100 mg	227.95 (182.36 ~ 227.95)	Gamma	(41, 43)
Sugemalimab/600 mg	1,945 (973 ~ 1,945)	Gamma	(41, 43)
Nivolumab/100 mg	1454.18 (727.09 ~ 1454.18)	Gamma	(41, 43)
Nedaplatin/50 mg	47.05 (42.74 ~ 51.36)	Gamma	(41, 43)
Carboplatin/100 mg	8.13 (8.13 ~ 8.65)	Gamma	(41, 43)
Cisplatin /10 mg	1.47 (1.38 ~ 1.47)	Gamma	(41, 43)
Cisplatin /30 mg	3.01 (3.01 ~ 4.40)	Gamma	(41, 43)
Docetaxel/20 mg	3.55 (3.54 ~ 8.51)	Gamma	(41, 43)
Paclitaxel/100 mg	27.98 (27.98 ~ 27.98)	Gamma	(41, 42)
Paclitaxel/30 mg	10.57 (10.57 ~ 10.57)	Gamma	(41, 42)
Albumin paclitaxel/100 mg	109.73 (109.72 ~ 109.73)	Gamma	(41, 43)
Gemcitabine/200 mg	9.43 (9.42 ~ 9.43)	Gamma	(41, 42)
Best supportive care/cycle	337.95 (270.36 ~ 405.54)	Gamma	(50)
Cost of end-of-life	2325.75 (1860.6 ~ 2790.9)	Gamma	(50)
Market shares			
Paclitaxel	0.61 (0.49 ~ 0.73)	Beta	(47)
Carboplatin	0.74 (0.59 ~ 0.89)	Beta	
Cost of follow-up and monitoring/$			
Cost of CT examination/1 time	58.17 (45.99 ~ 68.98)	Gamma	(44)
Cost of blood biochemical examination/1 time	47.05 (37.2 ~ 55.8)	Gamma	(44)
Cost of blood test/1 time	3.14 (2.49 ~ 3.73)	Gamma	(44)
Cost of urinalysis/1 time	0.63 (0.5 ~ 0.75)	Gamma	(44)
Cost of diagnosis/	3.14 (1.55 ~ 4.66)	Gamma	(44)
Cost of intravenous injection/1 time	1.73 (1.55 ~ 2.14)	Gamma	(44)
Cost of nursing/1 time	3.77 (2.98 ~ 4.47)	Gamma	(44)
Cost of bed/1 time	6.6 (5.22 ~ 7.83)	Gamma	(44)
Cost of grade 3–5 adverse events/$			
Neutropenia	116.37 (51.11 ~ 357.8)	Gamma	(47)
Decreased platelet count	1523.82 (1240.17 ~ 1771.67)	Gamma	(47)
Anemia	140.4 (106.73 ~ 160.1)	Gamma	(47)
Leukopenia	116.37 (51.11 ~ 357.8)	Gamma	(47)
Pneumonia	1,640 (1,312 ~ 1,968)	Gamma	(26)
Hyponatremia	3,223 (2578.4 ~ 3867.6)	Gamma	(49)
Asthenia	107 (80 ~ 134)	Gamma	(51)
Utility-related parameters			
Utilities for each state (base-case analysis)			
Progression-free survival (immunotherapy)	0.75 (0.71 ~ 0.85)	Beta	(47)
Progression-free survival (chemotherapy)	0.70 (0.66 ~ 0.80)	Beta	(47, 52, 53)

(Continued)

TABLE 1 (Continued)

Item	Mean (range)	Distribution	Sources
Progression disease	0.59 (0.47 ~ 0.71)	Beta	(47)
Utilities for each state (scenario 1)			
Progression-free survival	0.804 (0.764 ~ 0.844)	Beta	(54)
Progression disease	0.321 (0.305 ~ 0.337)	Beta	(54)
Utilities for each state (scenario 2)			
Progression-free survival (immunotherapy)	0.877 (0.850 ~ 0.904)	Beta	(52)
Progression-free survival (chemotherapy)	0.823 (0.775 ~ 0.871)	Beta	(52)
Progression disease (second-line treatment)	0.768 (0.721 ~ 0.815)	Beta	(52)
Progression disease (third-line treatment)	0.703 (0.632 ~ 0.774)	Beta	(52)
Disutilities for grade 3–5 adverse events			
Neutropenia	0.2 (0.16 ~ 0.24)	Beta	(47)
Decreased platelet count	0.11 (0.09 ~ 0.13)	Beta	(47)
Anemia	0.07 (0.06 ~ 0.09)	Beta	(47)
Leukopenia	0.2 (0.16 ~ 0.24)	Beta	(47)
Pneumonia	0.05 (0.04 ~ 0.06)	Beta	(26)
Hyponatremia	0.08 (0.06-0.1)	Beta	(49)
Asthenia	0.07 (0.06 ~ 0.08)	Beta	(54)
Other			
Discount	0.05 (0.00–0.08)	Beta	(55)

N + C, Nedaplatin in combination with standard chemotherapy; SI + C, Sintilimab in combination with standard chemotherapy; P + C, Pembrolizumab in combination with standard chemotherapy; T + C, Tislelizumab in combination with standard chemotherapy; CA + C, Camrelizumab in combination with standard chemotherapy; SU + C, Sugemalimab in combination with standard chemotherapy. † Average of five first-line randomized controlled trials; ‡ No sq-NSCLC subgroup safety data from Checkmate-078 China (54).

Orient-11 (56) by mapping to the EuroQol-5-dimension-5 level (EQ-5D-5L) (47). According to Shen et al. (52) and Nafees et al. (54), the utilities of patients receiving chemotherapy for PFS were 0.05 smaller than the utilities of those receiving immunotherapy. The EQ-5D utilities were 0.75 (immunotherapy) and 0.70 (chemotherapy) for PFS, and 0.59 for first- or end-stage PD. Considering the uncertainty of utilities which may have significant influences on the results, we used the utilities of Shen et al. (52) and Nafees et al. (54) to conduct two additional scenario analyses. The utility of the death state was specified as 0. Disutilities of AEs were extracted from other studies of Chinese patients. More details are shown in Table 1.

Cost-effectiveness analysis

We evaluated the cost-effectiveness of these strategies from the Chinese healthcare system perspective, the simulated cohort was modeled for 20 years, at which point the mortality rate was 99%, which is the lifetime horizon recommended (55). The expected costs and quality-adjusted life years (QALYs) for each treatment were derived by assigning the corresponding costs and utilities to the time patients in each health state. Cost-effectiveness was measured by the incremental cost-effectiveness ratio (ICER) and incremental net monetary benefit (INMB). Recommended according to China Guidelines for Pharmacoeconomic Evaluations (55), a range of willingness-to-pay (WTP) thresholds, from USD 12,728–38,184 per QALY gained, that is, 1–3 times the gross domestic product (GDP) per capita. While domestic scholars have basically reached a consensus that the threshold limit of three times per capita GDP doesn't apply to China. Recently, Cai et al. (57) found the cost-effective threshold of a QALY in China was close to 1.5 times of GDP per capita (USD 19,091). Thus, in the base-case analysis, USD 19,091 was used to investigate whether alternative treatments were more cost-effective. National Institute for Health and Clinical Excellence (NICE) recommended multiplying the threshold level for end-stage disease treatment by a factor of 1.7, thus we used the cost-effective threshold of 2.55 times the GDP (USD 32,456) per capita in the subgroup analysis for second-line drugs (58). As recommended (55), costs and utilities were both discounted at an annual rate of 5% to reflect present values.

Subgroup analysis

In addition to exploring the optimal treatment sequences, we also conducted subgroup analysis of the cost-effectiveness between first-line or second-line treatments. For the first-line subgroup, we compared seven treatments (standard chemotherapy, N + C, P + C, T + C, CA + C, SI + C or SU + C); For the second-line subgroup, we compared three treatments (nivolumab, tislelizumab, and docetaxel).

Sensitivity analysis

Sensitivity analysis was performed to address the uncertainties in parameter values and decision making. We performed a one-way sensitivity analysis to test the sensitivity of results to changes in parameters such as costs, treatment effects, and utilities. Tornado graphs were plotted with the INMB used as a measure of cost-effectiveness to visualize the parameters which had a meaningful association with the conclusion. A Monte Carlo simulation was performed for 10,000 iterations for the probabilistic sensitivity analysis (PSA). The Gamma distribution was selected for cost, the Beta distribution for probability, proportion, and utilities, the Log-normal distribution was selected for the NMA shape or scale parameters. All the parameters were adjusted within the reported 95% confidence intervals or assuming reasonable ranges of the base-case values, details are provided in Table 1. A Scatter plot was drawn using the average cost and utility of 10,000 simulations for each therapy; cost-effectiveness acceptability curves were used to analyze the cost-effectiveness for each regimen with various cost-effective thresholds.

Scenario analysis

To further explore the influence of parameter uncertainty and model structure on the research results, the following five scenarios were analyzed in this study.

Scenario 1: Using the utilities from Nafees et al. (54), the EQ-5D utilities were 0.804 for PFS and 0.321 for first- or end-stage PD.

Scenario 2: Using the utilities from Shen et al. (52), the EQ-5D utilities were 0.877 (immunotherapy) and 0.823 (chemotherapy) for PFS, 0.768 and 0.703 for first- or end-stage PD.

Scenario 3: Patient assistance programs (PAP) were considered for sugemalimab, nivolumab and pembrolizumab. Details are provided in Supplementary material 2.

Scenario 4: Considering the impacts of research time limits, longer simulation time frames, while closer to patients' lifetime costs and outcomes, also introduced more uncertainty. Therefore, we compared the costs and effects of each treatment when the simulation time was 5, 10 and 20 years.

Scenario 5: The cost of the third-line treatment the base-case analysis may be different from the actual clinical situation. For example, for patients with PS 0-1, third-line treatment with nivolumab or paclitaxel are recommended (21). We assumed that the cost of third-line treatment changed from USD 0–4,000 per cycle in this scenario.

Results

Network meta-analysis and survival rates estimates

A total of eight clinical trials with 2,154 patients were included in our NMA: Keynote-407 China, CameL-sq, Orient-12, Gemstone-302, Just and Rationale-304 for the first-line NMA (10–13, 16, 20); Checkmate-078 China and Rationale-303 for the other two second-line NMAs (23, 24, 46). Details for search strategies, network plot and risk of bias assessment are provided in Supplementary material 2, information of all RCTs are presented in Supplementary material 1. We chose the first-order FP models ($P = -2$) for the first-line NMA and the second-line NMA for PFS, second-order FP model ($P_1 = -0.5$, $P_2 = 0$) for the second-line NMA for OS. Related parameters for each intervention are listed in Table 1. The survival curves fitted by all models are provided in Supplementary material 2. The log-logistic model was chosen to reconstruct PFS curves of standard chemotherapy. The exponential distribution and restricted cubic spline models were used to fit the OS and PFS curves 'of docetaxel, respectively. Details of the fitted survival curves for all treatments of the different models are provided in Supplementary material 2. AICs for parametric survival models are shown in Supplementary material 2. Other details for selecting parametric survival models are presented in Supplementary material 2. The PFS and OS curves of all first- or second-line treatments finally used in our model are presented in Figure 2.

Model validation

The validation results showed that our model fitted and extrapolated well, and were consistent with clinical practice. Details results of model validation are presented in Supplementary material 2.

Base-case analysis

The results of the base-case analysis are shown in Table 2. The mean QALYs for patients who received CD, ND, TID, SID, CT, NT, CN, NN, CAD, NN, CN, SUD or PED were 0.866, 0.906, 1.179, 1.266, 1.283, 1.301, 1.353, 1.389, 1.603, 1.721 and 1.807 ranked from least to most effective. The mean costs for patients who received ND, CD, SID, TID, NT, CT, CAD, NN, CN, SUD, and PED were USD 9,900, 9,981, 15,855, 16,072, 17,765, 18,131, 19,026, 61,498, 62,227, 80,927 and 117,369, ranked from least to most costly. Compared with ND, CD, SID, TID, NT and CT, the ICERs of CAD were USD 13,096, 12,276, 9,421, 6,974, 4,183, and 2,804 per QALY, all were <USD 19,091; and compared with NN and CN, CAD was cost-saving with improved effectiveness. The ICER of SUD and PED were USD 522,023 and 481,639 per QALY compared with CAD, respectively. Therefore, CAD was considered to be the most cost-effective treatment path for advanced sq-NSCLC, followed by SID, ND, NT, CD, TID, CT, NN, CN, SUD and PED in that order. Breakdown results of costs and utilities are shown in Supplementary material 3.

Subgroup analysis

Cost-effectiveness of first-line therapies

Compared with CA + C, the INMBs for the other 6 options were USD−3255 (SI + C),−4178 (N + C),−5134 (T + C),−47,971 (standard chemotherapy),−59,637 (SU + C) and−94,444 (P + C), from most cost-effective to least. Details are provided in

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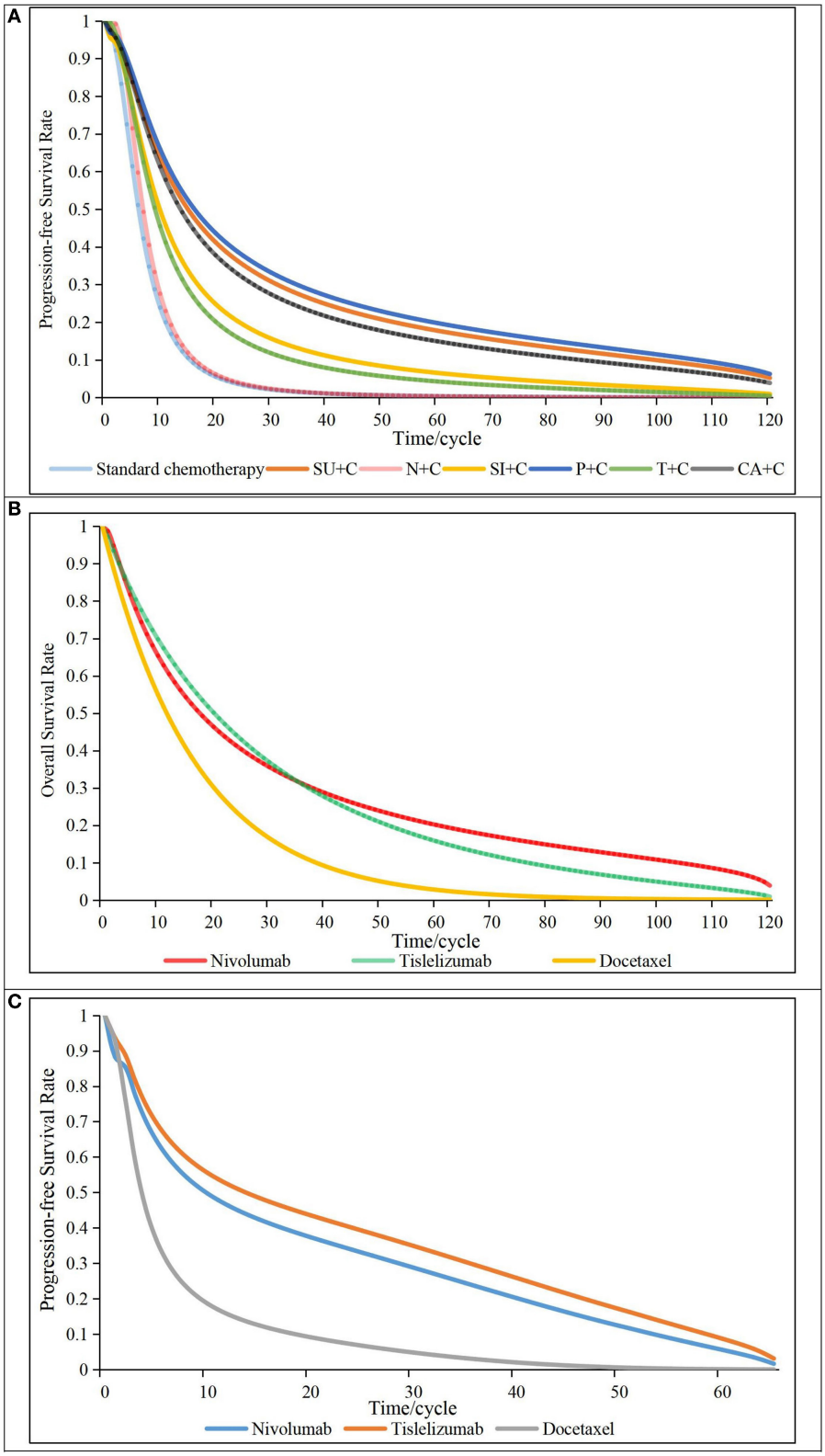

FIGURE 2
Survival curves of all first- or second-line treatments. **(A)** progressive-free survival curves for first-line treatments (above), **(B)** overall survival curves for second-line treatments (middle), **(C)** Progressive-free survival curves for second-line treatments (below), N + C, Nedaplatin in combination with standard chemotherapy; SI + C, Sintilimab in combination with standard chemotherapy; P + C, Pembrolizumab in combination with standard chemotherapy; T + C, Tislelizumab in combination with standard chemotherapy; CA + C, Camrelizumab in combination with standard chemotherapy; SU + C, Sugemalimab in combination with standard chemotherapy; cycle, 21 days.

TABLE 2 Base-case analysis results.

Treatment	ND	CD	SID	TID	NT	CT	CAD	NN	CN	SUD	PED
Cost/$ (95% CI, discounted)	9,900 (9,775∼10,030)	9,981 (9,859∼10,109)	15,855 (15,706∼16,018)	16,072 (15,910∼16,244)	17,765 (17,542∼18,003)	18,131 (17,906∼18,372)	19,026 (18,846∼19,228)	61,498 (60,393∼62,625)	62,227 (61,102∼63,376)	80,927 (79,959∼81,919)	117,369 (115,979∼118,785)
Utility/QALYs (95% CI, discounted)	0.906 (0.894∼0.917)	0.866 (0.854∼0.877)	1.266 (1.247∼1.285)	1.179 (1.162∼1.196)	1.301 (1.283∼1.319)	1.283 (1.265∼1.301)	1.603 (1.578∼1.627)	1.389 (1.368∼1.410)	1.353 (1.331∼1.374)	1.721 (1.695∼1.747)	1.807 (1.779∼1.834)
Life-years/years (95% CI)	1.475 (1.454∼1.495)	1.424 (1.404∼1.445)	1.991 (1.960∼2.021)	1.858 (1.830∼1.885)	2.241 (2.207∼2.274)	2.219 (2.185∼2.253)	2.513 (2.473∼2.554)	2.435 (2.393∼2.476)	2.340 (2.338∼2.421)	2.700 (2.658∼2.743)	2.834 (2.789∼2.879)
NMB/$ (95%CI, discounted)[¶]	7,391 (7,270∼7,510)	6,548 (6,424∼6,667)	8,315 (8,082∼8,535)	6,436 (6,257∼6,604)	7,073 (6,931∼7,200)	6,368 (6,222∼6,496)	1,1569 (11,247∼11,871)	−3,4979 (-35928∼-34,051)	−36,401 (-37370∼-35,456)	−48,068 (-48703∼-47,456)	−82,875 (-83902∼-81,880)
INMB (VS. CAD)	−4,178	−5,022	−3,255	−5,134	−4,496	−5,201	NA	−46,548	−47,971	−59,637	−94,444
ICER	VS. ND	VS. CD	VS. SID	VS. TID	VS. NT	VS. CT	VS. CAD	VS. NN	VS. CN	VS. SUD	–
CD	dominated	–	–	–	–	–	–	–	–	–	–
SID	16,530[†]	14,677[†]	–	–	–	–	–	–	–	–	–
TID	22,590[§]	19,450[§]	−2486.48	–	–	–	–	–	–	–	–
NT	19,897[§]	17,884[†]	54,567	13,869[†]	–	–	–	–	–	–	–
CT	21,802[§]	19,522[§]	131,978	19,738[§]	dominated	–	–	–	–	–	–
CAD	13,096[†]	12,276[‡]	9,421[‡]	6,974[‡]	4,183[‡]	2,804[‡]	–	–	–	–	–
NN	106,754	98,453	370,975	216,196	496,744	409,928	dominated	–	–	–	–
CN	117,048	107,285	534,502	265,508	858,964	634,344	dominated	dominated	–	–	–
SUD	87,102	82,941	142,968	119,609	150,331	143,401	522,023	58,502	50,761	–	–
PED	119,270	114,123	187,726	161,344	196,940	189,562	481,639	133,753	121,458	425,698	–

[†] <1.5 times 2021 Gross Domestic Product (GDP) per capita ($19,092); [‡] 1 times the 2021 GDP per capita ($12,728); [§] <3 times the 2021 GDP per capita ($38,184); [¶]Cost-effective threshold = 1.5 times the 2021 Gross Domestic Product per capita ($19,092). NMB, net monetary benefit (at the willingness to pay threshold of 1.5 times GDP per capita); INMB, increased net monetary benefit; NN, first-line nedaplatin-based chemotherapy followed by second-line nivolumab; NT, first-line nedaplatin-based chemotherapy followed by second-line tislelizumab; ND, first-line nedaplatin-based chemotherapy followed by second-line docetaxel; CN, first-line standard chemotherapy followed by second-line nivolumab; CT, first-line standard chemotherapy followed by second-line tislelizumab; CD, first-line standard chemotherapy followed by second-line docetaxel; TID, first-line tislelizumab combined with chemotherapy followed by second-line docetaxel; CAD, first-line camrelizumab combined with chemotherapy followed by second-line docetaxel; PED, first-line pembrolizumab combined with chemotherapy followed by second-line docetaxel; SID, first-line sintilimab combined with chemotherapy followed by second-line docetaxel; SUD, first-line sugemalimab combined with chemotherapy followed by second-line docetaxel; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; INMB, Incremental net monetary benefit; CI, confidence interval.

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Supplementary material 3. The NMB of CA + C was the largest among the seven treatments, which suggested that CA + C was the most cost-effective option.

Cost-effectiveness of second-line therapies

Tislelizumab with the largest NMB and QALYs among the three options was the most economical and effective second-line therapy for patients receiving either standard chemotherapy or nedaplatin in the first-line. Compared with docetaxel, the ICER of tislelizumab was about 1.5 times the GDP per capita per QALY, which was much smaller than that of nivolumab (USD 106,969/QALY). Other details are provided in Supplementary material 3.

Sensitivity analysis

One-way sensitivity analysis

Selecting the most economical CAD as the reference, we made tornado graphs of the other 10 treatment sequences (Figure 3). Although each parameter fluctuated, the NMBs of CAD were always larger compared with NN, CN, PED and SUD. Only when the HRs for PFS of CA + C fluctuated, CD, ND, CT and TID were likely to be more cost-effective. The cost-effectiveness of CAD and SID were affected by HRs for PFS of CA + C and SI + C, and cost-effectiveness of CAD and NT were affected by HRs for PFS of CA + C and OS of tislelizumab. One-way sensitivity analysis indicated that the HRs and costs of immunotherapy drugs had the greatest impacts on the INMBs, but overall, the base-case analysis results were relatively stable.

Probabilistic sensitivity analysis

The results of the PSA are shown in Figure 4. The scatter plot showed that NN, CN, SU and PE were not cost-effective even when cost-effective threshold was three times the GDP per capita compared to CD; the ICERs of the other six treatment sequences (ND, TID, SID, NT, CT, and CAD) were below the chosen cost-effective threshold compared to CD. Compared with the other six treatments, the ICERs of CAD were all much smaller than the chosen cost-effective threshold. According to the cost-effectiveness acceptability curves, ND was the most economical option when cost-effective threshold was lower than USD 15,000, and CAD was the most economical therapy when cost-effective threshold was over USD 15,000. Under the chosen threshold, CAD was the optimal choice in cost-effectiveness. These results confirmed that the conclusions of our study were sufficiently reliable.

Scenario analysis

Results of Scenarios 1–4 are concluded in Supplementary material 3. In the first two scenarios, when utilities changed, the ICERs of CAD compared with economically suboptimal ND and SID both became smaller, even <2,021 GDP per capita. After considering PAP, cost of sugemalimab, nivolumab, or pembrolizumab was all much lower, ICER of nivolumab, sugemalimab or pembrolizumab was $40,726, 34,094, and 24,499 compared to the ND, while still exceeded the selected cost-effective threshold. When the study time frame was reduced to 5 or 10 years, the ICER for CAD compared to ND increased slightly, but overall results were similar to those of 20 years. According to Supplementary material 3, CAD was always the most cost-effectiveness option over time. Results of Scenario 5 (Supplementary material 3) showed that the cost of third-line therapy did not affect the cost-effectiveness of CAD.

Discussion

We explored the effectiveness and cost-effectiveness of different regimens for advanced sq-NSCLC treatment. According to the recommendation of CSCO 2022, 11 treatment sequences (ND, NN, NT, CD, CT, CN, TID, CAD, PED, SUD, and SID) are available for patients with advanced sq-NSCLC. We evaluated the effectiveness and cost-effectiveness of these treatment from the perspective of Chinese healthcare system using a sequential model. We found that regardless of using in the first- or second-line, immunotherapy would bring higher cost but more survival benefits to patients than chemotherapy. The base-case results showed that PED was the most effective option, but CAD was the optimal choice in cost-effectiveness under the chosen cost-effective threshold of 1.5 times the GDP per capita. Compared with suboptimal therapies, ND and SID, the ICERs of CA + C + D were USD 13,096 and 9,421 per QALY, respectively. Both one-way and probabilistic sensitivity analyses confirmed that the results were sufficiently reliable, CAD was the most cost-effective therapy when this is not a commonly used acronym in health economics. was over USD 15,000. Scenario analysis showed that CAD was always the most cost-effective, regarless of the changes in utilities, study duration, PAP, and cost of third-line treatment.

Subgroup results showed that P + C was the most effective, while CA + C was the most cost-effective among seven first-line therapies. Tislelizumab was the best second-line choice compared to nivolumab and docetaxel both in effectiveness and cost-effectiveness.

PED and SUD were the most effective treatment sequences, which could bring 1.807 and 1.721 QALYs to patients, respectively. But pembrolizumab and sugemalimab were cost-effective compared to CAD only after a price reduction of 90 and 85% respectively. Keynote-407 China (13) was chosen as the source of the efficacy of P + C in this China-based research. Compared with the global population (14), the performance of P + C in the Chinese population improved a lot, which was the reason why P + C was so effective in this study.

No studies targeted on the cost-effectiveness of treatment sequences for advanced sq-NSCLC in China have been published so far. Cheng et al. (22) explored the cost-effectiveness of atezolizumab compared with chemotherapy in treating NSCLC patients with PD-L1 expression levels >50%. The authors concluded that atezolizumab had better efficacy but was not cost-effective. Teng et al. (59) compared nivolumab, pembrolizumab, atezolizumab, and durvalumab in first-line treatment of NSCLC patients with high PD-L1 expression. The effectiveness and cost-effectiveness of nivolumab were found to be similar among various immune checkpoint inhibitors, but nivolumab was the most economical.

FIGURE 3
Tornado diagram showing the results of the deterministic sensitivity analysis. NN, first-line nedaplatin-based chemotherapy followed by second-line nivolumab; NT, first-line nedaplatin-based chemotherapy followed by second-line tislelizumab; ND, first-line nedaplatin-based chemotherapy followed by second-line docetaxel; CN, first-line standard chemotherapy followed by second-line nivolumab; CT, first-line standard chemotherapy followed by second-line tislelizumab; CD, first-line standard chemotherapy followed by second-line docetaxel; TID, first-line tislelizumab combined

(Continued)

FIGURE 3 (Continued)
with chemotherapy followed by second-line docetaxel; CAD, first-line camrelizumab combined with chemotherapy followed by second-line docetaxel; PED, first-line pembrolizumab combined with chemotherapy followed by second-line docetaxel; SID, first-line sintilimab combined with chemotherapy followed by second-line docetaxel; SUD, first-line sugemalimab combined with chemotherapy followed by second-line docetaxel; HR, hazards rations; OS, overall survival; PFS, progression-free survival; PD, progression disease; Cam, camrelizumab; Tis, tislelizumab; Niv, nivolumab; Che, Chemotheraphy; Dox, docetaxel; BSC, best support care; IM, immunotheraphy; Sug, sugemalimab; Sin, sintilimab; Pem, pembrolizumab; CT, computed tomography; AE, adverse events.

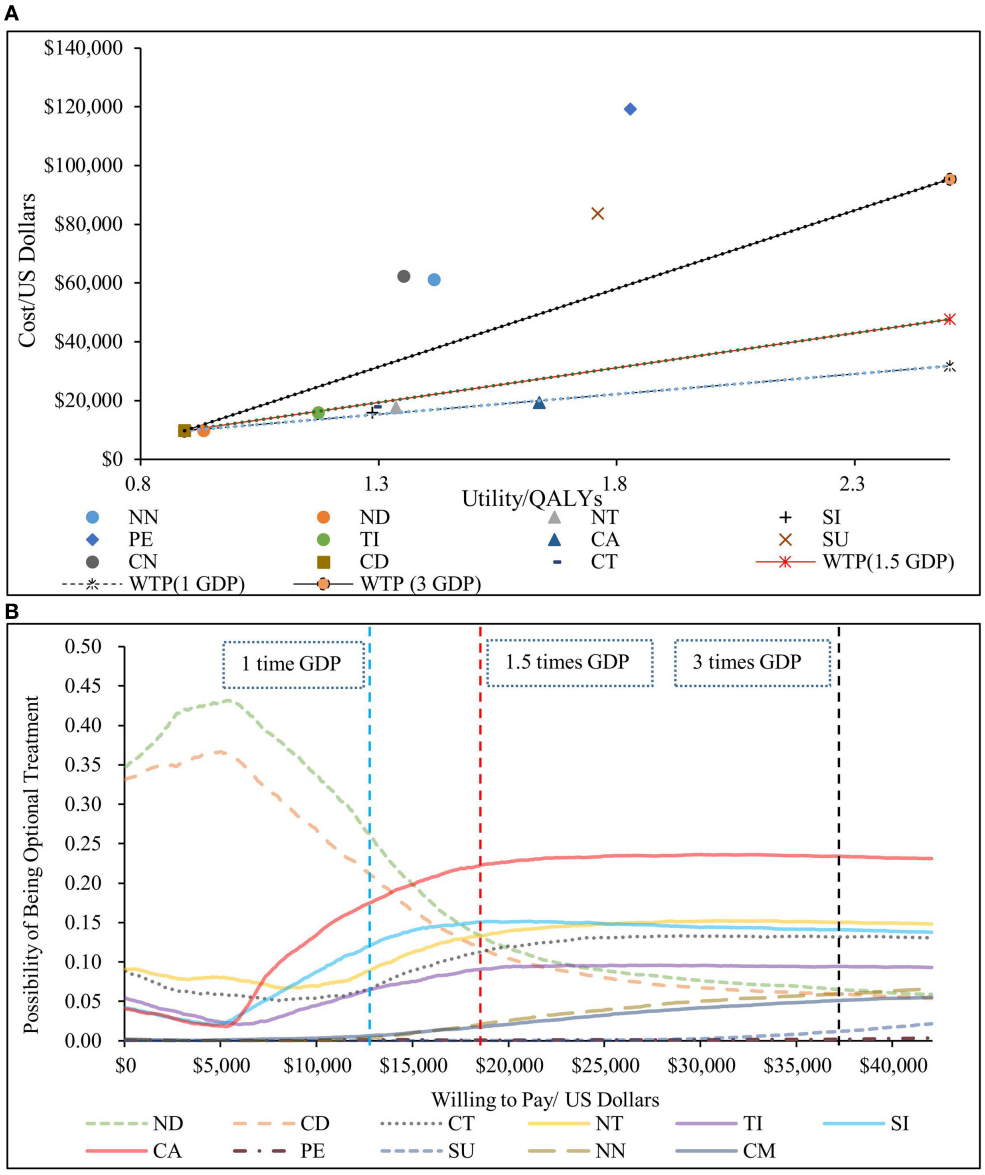

FIGURE 4
Results of the probabilistic sensitivity analysis. **(A)** scatter plot (above). **(B)** cost-effectiveness acceptable curve (below). NN, first-line nedaplatin-based chemotherapy followed by second-line nivolumab; NT, first-line nedaplatin-based chemotherapy followed by second-line tislelizumab; ND, first-line nedaplatin-based chemotherapy followed by second-line docetaxel; CN, first-line standard chemotherapy followed by second-line nivolumab; CT, first-line standard chemotherapy followed by second-line tislelizumab; CD, first-line standard chemotherapy followed by second-line docetaxel; CA, first-line camrelizumab combined with chemotherapy followed by second-line docetaxel; PE, first-line pembrolizumab combined with chemotherapy followed by second-line docetaxel; SI, first-line sintilimab combined with chemotherapy followed by second-line docetaxel; SU, first-line sugemalimab combined with chemotherapy followed by second-line docetaxel; QALY, quality-adjusted life year; GDP, 2021 per capita Gross Domestic Product.

Hao et al. (60) showed that nivolumab combined with ipimumab was not cost-effective compared with chemotherapy in advanced EGFR or ALK mutation-negative NSCLC. Wu et al. (61) evaluated the combination of pembrolizumab with chemotherapy and chemotherapy in patients with EGFR or ALK mutation-negative sq-NSCLC, and showed that the combination regimen

was not cost-effective regardless of the PD-L1 expression level. Liao et al. (62) further confirmed from the perspective of the whole society that pembrolizumab was not economical compared to chemotherapy for PD-L1 High-expressing NSCLC. Further information of a systematic review of current published CEA based in China is provided in Supplementary material 1.

Sintilimab, camrelizumab and tislelizumab have been included in the NRDL since 2020, which meant that the prices of these drugs had greatly reduced, thereby improving the cost-effectiveness of combination therapy (41, 43). Camrelizumab combined with chemotherapy for first-line treatment or and tislelizumab for second-line treatment of advanced sq-NSCLC is likely to be listed in the NRDL based on the results of CameL-sq and Rationale-303 (11, 46). As the prices of camrelizumab and tislelizumab were unclear for sq-NSCLC, we considered a wide range of prices, and the sensitivity analysis results showed that the prices did not affect the conclusion.

Strengths and limitations

Firstly, effectiveness and cost-effectiveness of seven first-line treatments, three second-line treatments and 11 treatment sequences for advanced sq-NSCLC approved in China were systematically compared for the first time. This study is important for patients, clinicians, and payers given the uncertainty about the optimal treatment for advanced sq-NSCLC, which causes serious morbidity and mortality in China. Our cost-effectiveness analysis provides information that can provide value-based decision-making evidence for the Chinese healthcare system. In the upcoming 2022 NRDL negotiation, our research may provide comprehensive and scientific evidence for drugs access negotiation for the treatment of wild-type advanced sq-NSCLC. Secondly, we constructed the NMA based on the FP model, and calculated time-varying HRs as non-PH were detected in the chosen trials. PH assumption has been used blindly without verification in previous studies, but actually this assumption is difficult to hold in NMA composed of multiple comparisons and serious survival fitting bias would be caused when PH models are used in case of PH assumption does not hold. Thirdly, we used a micro-simulation model that allows transition rates to vary over time under the time-reset option. Compared with memoryless hypothesis Markov cohort model, our model better simulated the long-term survival of patients. Finally, through sensitivity analysis and scenario analysis, we have fully explored the influences of parameter uncertainty and model structure on the results.

Our model includes several simplifying assumptions that limit its application. Firstly, to estimate progression rates, we synthesized survival data from multiple clinical trial populations. This introduced some uncertainty because no one trial population followed the treatment regimens specified in our model. Secondly, efficacy of docetaxel in patients receiving first-line immunotherapy is not yet available, and we assumed the efficacy of these patients were the same as receiving SC in first-line. According to the results of Checkmate 057 (63) and a real-world study (64), the median OS of advanced non-squamous NSCLC patients receiving docetaxel after standard chemotherapy was 9.5 (8.1–10.7) months, and the median OS of patients receiving docetaxel after treatment with immunotherapy combined with chemotherapy was 9.0 (8.1–11.2) months, thus, the efficacy of docetaxel was nearly identical whether received treatment with immunotherapy combined with chemotherapy or standard chemotherapy in first-line, and we considered our assumptions to be reasonable. Thirdly, there is no direct head-to-head evidence for the relative efficacy of N + C, P + C, SI + C, SU + C, CA + C and TI + C, and no direct evidence for the relative efficacy of tislelizumab and nivolumab, although we identified and used the best NMA model, some uncertainty remains. Fourthly, PFS rates of some first-line treatments such as SI + C and TI + C were relatively immature, parametric extrapolation would bring certain uncertainties. Fifthly, because the tail data of the PFS curves in the second-line docetaxel group were too sparse, the HRs calculated in the model were relatively small, which in turn caused the efficacy of tislelizumab and nivolumab to be slightly overestimated. Finally, toripalimab and penpulimab were not considered in our model, as they are second-level recommended by CSCO 2022 and have not yet been approved for treatment of sq-NSCLC in China as of May 2022.

Conclusion

We provided a novel sequential model to determine the optimal therapeutic pathway as certain reference for future research. Although PED is currently the most effective therapy, CAD is the most cost-effective treatment sequence among 11 options. P + C and CA + C is the most effective and cost-effective therapy in first-line, respectively; tislelizumab is the best second-line choice. Our results may help clinicians make optimal decisions in treating advanced sq-NSCLC and provide value-based evidence for decision-making for the Chinese healthcare system. However, long-term follow-up data and direct-comparison evidence are still needed to confirm the results.

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

WT, MZ, and TS: full access to all of the data in the study, take responsibility for the integrity of the data, the accuracy of the data analysis, and concept and design. MZ, TS, and ZC: acquisition of data. MZ: analysis and interpretation of data. WT, MZ, TS, and ZC: critical revision of the manuscript for important intellectual content. MZ and TS: statistical analysis and drafting of manuscript. WT: obtaining funding, administrative and technical support, and supervision. All authors contributed to the article and approved the submitted version.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1051484/full#supplementary-material

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Glossary

AE, Adverse Reaction; AIC, Akaike Information Criterion; BSC, Best Supportive Treatment; CHEERS, Consolidated Health Economic Evaluation Reporting Standards; CSCO 2022, Chinese Society of Clinical Oncology Guidelines 2022; EORTC QLQ-C30, European Organization for Research and Treatment Quality of Life Questionnaire-Core 30; EQ-5D, Euroqol-5-Dimension; EQ-5D-5L, Euroqol-5-Dimension-5 Level; CAD, First-Line Ca + C Followed By Second-Line Docetaxel; ND, First-Line N + C Followed By Second-Line Docetaxel; NN, First-Line N + C Followed By Second-Line Nivolumab; NT, First-Line N + C Followed By Second-Line Tislelizumab; PED, First-Line P + C Followed By Second-Line Docetaxel; SID, First-Line Si + C Followed By Second-Line Docetaxel; CD, First-Line Standard Chemotherapy Followed By Second-Line Docetaxel; CN, First-Line Standard Chemotherapy Followed By Second-Line Nivolumab; CT, First-Line Standard Chemotherapy Followed By Second-Line Tislelizumab; SUD, First-Line Su + C Followed By Second-Line Docetaxel; TID, First-Line T + C Followed By Second-Line Docetaxel; FP, Fractional Polynomial; GDP, Gross Domestic Product; HR, Hazard Ratio; ICER, Incremental Cost-Effectiveness Ratio; INMB, Incremental Net Monetary Benefit; NRDL, National Reimbursement Drug List; N + C, Nedaplatin Combined With Docetaxel; NMA, Network Meta-Analysis; NSCLC, Non-Small Cell Lung Cancer; non-sq, Non-Squamous; OS, Overall Survival; CA+C, Paclitaxel And Platinum Combined With Camrelizumab; P + C, Paclitaxel And Platinum Combined With Pembrolizumab; SU + C, Paclitaxel And Platinum Combined With Sugemalimab; T + C, Paclitaxel And Platinum Combined With Tislelizumab; PAP, Patient Assistance Program; PS, Performance Status; SC, Platinum-And Paclitaxel-Based Chemotherapy; SI + C, Platinum Combined With Gemcitabine And Sintilimab; PD-1, Programmed Death-1; PD-L1, Programmed Death-Ligand 1; PD, Progressed Disease; PFS, Progression-Free Survival; PH, Proportional Hazard; QALY, Quality-Adjusted Life Year; RCT, Randomized Clinical Trial; RP, Royston and Parmar; sq, Squamous; USD, United States Dollars; WTP, Willingness-To-Pay.

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Early palliative care for solid and blood cancer patients and caregivers: Quantitative and qualitative results of a long-term experience as a case of value-based medicine

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Introduction: Cancer patients and their caregivers have substantial unmet needs, that negatively impact the clinical outcome and quality of life. However, interventions aimed to address such needs are still suboptimal, failing to answer the recent healthcare call for the adoption of value-based models of care. In the case of incurable oncologic and hematologic cancers, a value-based model of care should plan advanced care on patients' needs and include the quality of death as an outcome. The integration of early palliative care into standard oncologic care for patients with advanced cancers represents a recent innovative model of assistance whose benefits for patients and caregivers are now widely recognized. The key elements underlying the reasons behind these benefits are the multidisciplinary collaboration (teamwork), an honest and empathetic communication between the early palliative care team, the patient, and the caregiver (rapport building), and the ability to detect changes in the physical/psychosocial wellbeing of the patient, along the whole disease trajectory (constant monitoring).

Methods: This community case study documents the quantitative and qualitative results of a long term clinical and research experience in delivering early palliative care service to address both solid and blood cancer patients' and their primary caregivers' needs.

Results: Data showed decreased use of chemotherapy, blood transfusions and referral to intensive care units near the end of life; increased life expectancy; improved symptom burden and mood; increased frequency of goals-of-care and advanced care planning conversations. Hope perception among bereaved caregivers was associated with resilience and realistic expectations raising from honest communication with the early palliative care team and appreciation toward the model. Patients and caregivers perceived the possibility of a good death as realistic and not as an unlikely event as it was for patients and caregivers on standard oncologic care only. Gratitude expressions toward the model and the team were frequently identified in their reports and positively associated with communication and spirituality.

Conclusions: These findings are discussed in the context of an updated literature review regarding value-based care and suggest that early palliative care integrated into standard oncology care may be considered as an effective model of value-based care.

KEYWORDS

early palliative care, advanced care, communication, value-based care, cancer

1. Introduction

With the advances in oncologic treatments, life expectancy for patients diagnosed with cancer has increased (1); however, advanced solid malignancies and high-risk hematologic neoplasia remain largely incurable. In such a wide clinical scenario, physicians have to face a broad range of patients' needs including those associated with the side effects of the new drugs, those associated with the survivorship and those related to the management of incurable cancers (2–4).

A large body of evidence attempted to assess and address needs in patients with cancer. However, implementation of effective interventions has been suboptimal and unmet needs still represent a challenge in oncology and even more in hematology (5).

Mismatched care models that are inconsistent with patients' and caregivers' needs can potentially lead to poor clinical outcomes such as higher morbidity and mortality and reduced quality of life (QOL) as well as a high healthcare use and expenditure (6–8). This is becoming increasingly incompatible with the call for the adoption of value-based models of care.

Value-based healthcare proposes the combination of medical skills with patients' values to obtain the best outcome at the lowest cost. It combines the highest level of technical-scientific data (technical value) with patient preferences, concerns, expectations, and influences (personal value) and the use of resources in order to obtain the greatest advantage for the population (allocation value) (9, 10).

Ideally, a value-based model of oncology care should assess unmet needs with a flexible approach. Indeed, cancer-related symptoms and patients' needs fluctuate along the whole disease trajectory (4, 11, 12) and in relation to different solid and blood tumor types (13–17).

The unmet needs of patients can increase the level of caregiver burden (4, 18), leading caregivers themselves to experience unmet needs. Caregivers' unmet needs do not only decrease their own QOL, but also affect patients' health outcomes negatively (19–21).

In this scenario, a "paradox" related to the value-based models of care emerges in relation to the situation of patients with incurable oncologic or hematologic cancers: if value is determined by the proportion between health outcomes and the resources used to obtain them, how can value be defined when the obvious outcome is death and not the recovery of the patient?

A number of studies have described and identified connections between the concept of quality of care, QOL and, even, "quality of death and dying" [e.g., (22–28)]. The application of the questionnaire on the "Quality of Death and Dying" (QODD) by Curtis et al. (23) found relevant correlations between the highest QODD scores and factors such as dying at home, lower symptom burden, better symptom management, better communication with the healthcare team, improved satisfaction with treatments.

More recently, an innovative model of assistance, consisting of the integration of palliative care to standard oncological care (SOC) since the diagnosis of incurable cancers, has resulted in improved physical and psychological symptoms, QOL and, even, QOL at end of life (QOL-EOL), suggesting a long-term benefit from interdisciplinary early palliative care (EPC) on care throughout the illness (26).

We claim that in oncology, the integration of EPC to the SOC may represent a value-based model. EPC includes anticipated guidance about symptom management and thoughtful discussions on goals of care that engage individuals to consider their values and care preferences in a more patient-centered and less disease-centered environment than the standard oncologic care (29).

In the following sections, the paper documents the experience of delivering EPC to solid cancer and blood cancer patients in two outpatient clinics in Italy. This description argues that EPC treatments can be considered as a form of value-based care in oncology and puts forward the hypothesis that EPC interventions could actually favor the combination of QOL, quality of care along all the disease trajectory, and the quality of death.

2. Context in which the innovation occurs

The provision of EPC described in this paper takes place in two EPC units.

The first is located at the Oncology and Palliative Care Unit of the Civil Hospital in Carpi, within the Local Health Unit in Modena; the second, at the EPC clinic of the section of Hematology, Azienda Ospedaliero Universitaria Policlinico, University of Modena and Reggio Emilia.

In both units, the EPC program involves assessment and management of symptoms, support in decision making and future planning, facilitation of coping and providing physical and emotional support through periodic tutorial meetings with oncologists/hematologists and nurses, as well as the assessment of patients' prognostic awareness, which is considered a crucial element defining an EPC intervention (30).

Patients commonly admitted at the Carpi Unit have advanced solid cancer, i.e., distant metastases, late-stage disease and/or a prognosis of 6–24 months (31). In Modena, patients have mostly acute myeloid leukemia (AML) or multiple myeloma, but also patients with other high-risk hematologic malignancies receive EPC. In both cases, the intervention is defined as "early" when provided within 8 weeks from cancer diagnosis (31–33).

3. Detail to understand key programmatic elements

Despite the fact that it is not possible to identify a single reference model that explains all the possible EPC interventions and how they should be implemented (34), the overall structure of an EPC intervention has been described and summarized in a way that shows its main components and their rationale (33, 35–37).

The crucial components of this model can be summarized with three keywords: teamwork, rapport building, constant monitoring. As for "teamwork," this keyword refers to the style of care characterizing the collaboration between the SOC team and the EPC team: in this model, the two teams never stop cooperating. It also refers to the kind of work developed by the EPC team with all the other physicians and subspecialists involved in patients' care, in addition to other interdisciplinary team members that may be consulted if appropriate (e.g., social worker, spiritual care worker, occupational therapist, physiotherapist, etc.). Finally, it is the EPC team who involves the home-based services when discontinuation of disease-directed care is decided and routine oncology follow-ups cease.

The second keyword, "rapport building," is a complement to "teamwork" and, in a way, its precondition: rapport building between the EPC team, patients and their families is begun early on, at the very first encounter, during which focus is placed especially on coping and support. The team explores patients' and caregivers' understanding and expectations regarding the disease and palliative treatments; at this point, caregivers' needs are also addressed. The style of care in the EPC clinic aims at maintaining a supportive therapeutic atmosphere and building on rapport established during previous encounters. Thanks to this style of care, over time it is possible to progressively develop discussions about end of life (EOL) and resuscitation status, including in the discussion also patients' family members. Appropriate communication is clearly a fundamental ingredient for "rapport building."

"Constant monitoring" is at the same time possible because of rapport building and another one of its ingredients. Indeed, as previously mentioned, the needs of advanced cancer patients may change rapidly and the care team must be ready to assess them and decide appropriate interventions. The EPC intervention may entail from three to five visits in order to be considered completed, focusing on symptom management, coping, prognostic awareness, decision-making and EOL planning (35). A key element in EPC interventions is the assessment of pain and other relevant symptoms and coping abilities, which should occur frequently if not at every visit. Moreover, if the minimum for a complete EPC intervention amounts to at least 1 monthly visit for the first 4 months, it is true that after the first visit the care team and patients/caregivers remain in constant contact, in order to manage sudden needs or symptoms, thus avoiding unnecessary visits to the clinic or to the ER.

3.1. The interventions in Carpi and Modena

The EPC units in Carpi and Modena operate largely based on the model described by Zimmermann et al. (33) and Greer et al. (35). In particular, as far as the unit in Carpi is concerned, a retrospective observational study observed different clinical indicators for 292 advanced cancer patients consecutively admitted at the Unit between 2014 and 2017 and with at least three or more palliative care visits from the time of diagnosis (31). Patients were assigned to either "early palliative/supportive care" or "delayed palliative/supportive care" groups, based on the time elapsed between the diagnosis and the initiation of the palliative care, using 90 and 60 days as a cut-off in a primary and secondary analysis, respectively.

The study confirmed a favorable association between EPC intervention and the index of EOL aggressiveness represented by the administration of chemotherapy in the last 14, 30, and 60 days of life, respectively. Specifically, the frequency of chemotherapy use in the last 60 days of life was 3.4% in the early group and 24.6% in the delayed group. This result is in line with similar results reported in the literature (29, 38) and seems to be strongly favored by improved patient prognostic understanding and shared decision-making, especially in the phase of transitioning from disease-directed care to supportive care alone. Other relevant findings of this study are that patients with advanced cancer enrolled in an EPC program were likely to experience an increase in their survival length, with an estimated survival probability at 1 year of 74.5% in the early group and 45.5% in the delayed group, and - regardless of the timing of palliative care referral - were more likely to have home deaths, and were more likely to report improved symptom burden and mood, as assessed by the Edmonton Symptom Assessment Scale.

A similar observational, retrospective study was conducted at the Modena Unit, aiming to investigate the presence of quality indicators for palliative and EOL care on 215 patients affected by acute myeloid leukemia. All patients were on palliative care, which was defined early when patients received three or more visits or delayed when patients received only one or two visits. Patients with acute promyelocytic leukemia and those undergoing allogeneic hematopoietic stem cell transplantation were excluded. Indicators were abstracted through a comprehensive review of their hospital chart (32). The results are similar to those of the Carpi study: very few patients (2.7%) received chemotherapy in the last 14 days of life; none of them was admitted in the intensive care unit during the last month of life; approximately half of them (50.7%) died at home or in a hospice vs. 5.3% who died in an acute facility; more than 40% received either red cell (49.3%) nor platelet (41.3%) transfusions within 7 days of death. More than 70% (71.8%) of patients receiving EPC had goals of care discussions, and almost 60% (57.3%) had advance care planning conversations.

In relation to the interventions in Carpi and Modena, there are other three studies worth mentioning because they further explore benefits deriving from the EPC interventions as implemented in these two units. More specifically, these studies explore the perceptions of hope and death and the emergence of gratitude in patients and caregivers recruited in both units between July 2020 and June 2022. Patients involved in the studies had advanced cancer whereas caregivers had an alive and/or a deceased patient with advanced cancer. Their eligibility required at least four visits at the EPC unit, willingness to complete the task, and age $\geq$18 years. At the time of the enrollment, patients had a life expectancy of more than 6 months and were not on interim evaluations to be

referred to hospice or home care. The relevance of these studies is explained by the fact that the way patients and caregivers perceive hope and death, as well as the positive emotions arising, although unsolicited, after the EPC intervention, can make a huge difference on their QOL and quality of death and dying; moreover, there is a substantial lack of studies exploring these dimensions qualitatively and based on patients' and caregivers' perceptions (26, 39).

In the first study, hope perceptions among bereaved caregivers of onco-hematologic patients who received EPC were explored (40). The participants of this study were 36 primary caregivers (14 males, 22 females) of deceased onco-hematologic patients treated with EPC at the Carpi Unit ($n = 26$, caregivers of solid tumor patients) and at the Modena Unit ($n = 10$, caregivers of hematologic tumor patients). Open-ended questionnaires asking about caregivers' experience with EPC were administered to participants, 2 months to 3 years after a patient death. Definitions of hope in the caregivers' narratives were analyzed through a directed approach to content analysis (41), which is one of the best-known methods to conduct qualitative research in the medical sciences on textual data, often adopted when there exists research on a certain phenomenon. The Based on the coding categories identified in the existing literature, which capture the main functions of hope (i.e., hope as expectation, hope as resilience, hope as desire), the main results of this study show that caregivers perceived hope mainly as resilience and as expectations based on what they were told about the patients' clinical conditions. Their hope was bolstered by trusting relationships with the healthcare teams and EPC interventions were recalled as the major support for hope, both during the illness and after the death of the patient. Results were complemented with automated lexicographic analysis on the words "hope" and "desire," to characterize their use in primary caregivers' definition of hope versus its meaning in everyday use, by identifying their relevant combinatorial properties, i.e., their recurrence with adjectives, adverbs and prepositional phrases. The automated quantitative lexical analysis provided deeper insights into the links between the concepts of hope, truth, and trust, which, in the respondents' words, form a tight semantic cluster. These findings suggest that telling the truth about an incurable onco-hematologic disease and beginning EPC might be a combination of factors fostering the onset of hope in the setting of incurable cancer.

In the second study, perceptions of death among patients with advanced cancer receiving EPC and their caregivers were explored, following a mixed method analysis (42). In this case, qualitative and quantitative analyses (43–45) were performed on two databases: (a) transcripts of open-ended questionnaires investigating thoughts and feelings about the personal experience with the disease prior and during the EPC intervention and about possible changes in the perception and expectations of their future administered to 130 cancer patients receiving EPC, and to 115 primary caregivers of patients on EPC treated in the two above mentioned units; (b) texts collected from an Italian forum, containing instances of web-mediated interactions between patients and their caregivers. The quantitative analysis consisted of extracting the combinatorial properties of the word "death" from the two databases and representing the most frequent combinations of words by means of Sketch Engine, a platform commonly used by linguists, translators, and lexicographers to analyze the meaning of lexical entities through text mining functions. The qualitative analysis was performed on the combinatorial properties by considering the semantic context in which they appeared, with the aim to provide context for the interpretation of these results. The most interesting finding in this study shows that for patients and caregivers on EPC the word "death" has positive and actual connotations, i.e., it expresses an experience, whereas for the participants interacting on the forum, a "good death" is referred to as a wish or as a negated event. These findings suggest that EPC interventions may be among the factors that favor an increased acceptance of death among advanced cancer patients and their caregivers.

In the third study, the hypothesis that a feeling of gratitude might be commonly encountered among cancer patients and their caregivers on EPC was explored (39). Reports from 251 patients with advanced cancer on EPC ($N = 133$; 73 males, 60 female) and their caregivers ($N = 118$; 39 males, 77 females) describing their clinical experience with the EPC model were analyzed through a content analysis and a quantitative text analysis program, to identify and rank the sources of gratitude and to quantify the use of words associated to categories of interest (i.e., gratitude, communication, spirituality), respectively. The presence of explicit or implicit expressions of gratitude were found in most of the reports (92.5% and 82.2% for patients and caregivers, respectively). Moreover, the identified sources of gratitude were structural components of the EPC intervention, namely: successful physical symptom management (mentioned by 83.5% of patients and 78% of caregivers), emotional support (mentioned by 46.6% of patients and 39% of caregivers), empowerment from the conversations on EOL (mentioned by 33.8% of patients and 11% of caregivers), better information (mentioned by 24.1% of patients and 22% of caregivers), humanity (mentioned by 24.1% of patients and 22% of caregivers), and a familiar environment (mentioned by 12% of patients and 14.4% of caregivers). Finally, the emergence of gratitude in patients' reports was positively associated with references to communication with the palliative team ($r = 0.215$, $p = 0.026$) as well as to spirituality ($r = 0.612$, $p < 0.001$). These results suggest that EPC and the associated benefits would unintentionally elicit positive emotions that, based on the positive psychological wellbeing (46), may represent useful resources for patients and caregivers, as well as a potent predictor of improved health outcome. Of note, in all the aforementioned studies a certain style of communication appears in connection with the benefits deriving from EPC interventions.

Another relevant and unique characteristic of the interventions in Carpi and Modena is that the mean number of EPC visits is significantly higher than those of three to five reported in literature, strongly suggesting that patients are conducted along the entire disease trajectory.

Indeed, several cohort studies have reported that inpatient PC, by fostering death at home, increases QODD. Nonetheless, in a secondary analysis of a cluster-randomized trial of EPC in advanced solid cancer patients (47), there was no association between EPC and overall QODD and QOL-EOL, and EPC exerted a significant and large effect also on QOL-EOL only when additional palliative care were added along the trajectory of the disease (26).

Thus, by managing invalidating symptoms, cultivating the prognostic awareness, favoring patients' and caregivers' understanding of treatment progress, helping with decision-making, exploring patients' values and assisting in the promotion of advanced care planning, in Carpi and Modena EPC positively affects patients' and caregivers' QOL and, by providing support along the entire trajectory of cancer, fosters "quality of death and dying" for patients and their caregivers.

4. Discussion

Value-based healthcare is a relatively new approach, which "aims to increase the value that is derived from the resources available for a population" (48, 49). However, there is not yet a complete consensus among scholars regarding what should be considered "value" in healthcare (10, 49–51).

Moreover, from various studies that observed cases of implementation of the value-based healthcare model, it is emerging that a crucial factor, albeit the less measurable one, is the quality of information production and circulation among all the stakeholders involved in the creation, provision and assessment of healthcare. Indeed, the dissemination of a "value culture" (52) can only happen *via* effective education, which involves sharing information about value and how to obtain it. Also the major tenet of value-based healthcare–i.e., the consideration of which outcomes are relevant for patients (53)–implies taking into consideration patients' views and preferences, which again involves effective communication strategies. In particular, the stress on patient-centeredness and on patient involvement is probably the major strength and at the same time the major challenge for the implementation of value-based healthcare, because personal perceptions and preferences by definition fluctuate and are not easily formalized in the way that would be required by an effective managerial model; indeed, various studies highlight the fact that value based healthcare can only be effectively implemented if the whole system accepts to be redesigned according to the concept of "value" (51, 54, 55).

In this sense, the EPC model could be considered as an example of successful value-based healthcare provision. The provision of care in an EPC model necessarily implies spending time with patients and their families in order to: build the kind of relationship that will allow addressing difficult topics; understand patients' and caregivers' clinical needs; understand patients' and caregivers' psycho-social or spiritual needs that have an import on their wellbeing (33, 36, 37, 56).

Moreover, regarding the feasibility of value-based healthcare, scholars have identified six interdependent and mutually reinforcing steps toward a high-value healthcare delivery system (52, 57–59). These are: 1. Organize integrated practice units; 2. Measure costs and outcomes for every patient; 3. Move to bundled payment for the care cycle; 4. Integrate care delivery across separate facilities; 5. Expand excellent services across geography; 6. Enable a suitable information technology platform. The EPC model of care seems to satisfy at least four of these steps: in order to be called an EPC intervention, it requires that different units of practice are integrated, and it is able to integrate care delivery across separate facilities, for example when transitioning from disease-oriented care to home care (33) (points 1 and 4); it has also been shown to be a cost-effective model (60–63), although there are still few studies based on sufficiently big samples. Indeed, adopting value-based care supports health care providers in their decisions while focusing on the values of patients, leading to lower healthcare costs, regardless of professionals' concern with the cost of treatment (64) (point 2). As regards point 6, there is mounting evidence that digital health technology, in the form of platforms allowing the electronic collection of patient reported outcomes (PROs), can have a positive impact on the overall management of cancer patients. Indeed, two recent RCTs in patients with several types of cancer during chemotherapy showed that remote symptom monitoring with electronic PROs was associated with reduced symptom burden and improved HRQoL outcomes (65, 66). Remarkably, the systematic monitoring of PROs *via* web-based platforms, was also found to be associated with improved overall survival in patients with advanced cancers (67, 68). Finally, a study examining physicians' perceptions of usability and clinical utility of a digital health tool (GIMEMA-ALLIANCE platform) for ePRO monitoring in the real-life practice of patients with hematologic malignancies found that all hematologists participating in the study agreed or strongly agreed that the platform was easy to use, and 87%, agreed or strongly agreed that ePROs data were useful to enhance communication with their patients (69). These preliminary results support the clinical utility, from the perspectives of the treating hematologist, of integrating ePROs into routine cancer care of patients with hematologic malignancies, and could be implemented in the EPC interventions.

With regard to the specific meaning of "value" involved in the treatment of advanced/high risk cancer patients and their families, we suggest that EPC treatments may also be successful in achieving the three levels of quality described by Curtis et al. (23). QOL-EOL has been shown to be associated with a systematic use of integrated palliative care (70) and is mostly associated to lower or no use of palliative chemotherapy, which has been shown to worsen patients' QOL and quality of death (71, 72). Aggressive treatments at the EOL are also usually considered as signs of low quality of care (73–75); the integration of EPC has been shown to reduce aggressive measures at the EOL, thus promoting quality of care (75–81).

As for the quality of the dying experience, the analysis of responses to questionnaires about perceptions of hope and death at the EPC Units in Carpi and Modena testify to perceptions of high quality. In the future, these should be verified also by the use of the QODD questionnaire.

Although the kind of value that needs to be obtained in an EPC setting (QODD) may be different from the one that is called for in other clinical settings (mainly QOL), a certain approach to care could be used as a model to progressively implement a value-based model of care along the entire trajectory of the disease.

Future research in this area should also focus on grounding the EPC model in a theoretical frame. Each intervention provided in the EPC context and described in this work arises from a large amounts of empirical, real-life data, in a bottom-up fashion. However, its robustness and validity require to be supported and further confirmed also through a top-down approach in order to

define a univocal model whose use can be extended to different onco-hematology populations. This would be beneficial to the model, also in terms of the flexibility required to support different types and different stages of the disease, but also to be extended to most medical specialties dealing with serious illnesses and close to the EOL.

5. Acknowledgment of conceptual or methodological constraints

We acknowledge that the model described in this article may be difficult to implement due to a few conceptual and methodological constraints.

As for conceptual constraints, it has been observed that the integrated EPC model of care has been described only in a standardized form, thus leaving it to professionals to devise specific strategies that will allow its implementation in local systems (33).

In a methodological perspective, a significant constraint is represented by the limited awareness still observable in the population regarding the existence of EPC clinics; moreover, oncologists' hesitancy to refer patients to palliative care and specific training for clinicians may also hinder the implementation of the proposed model of care (82, 83).

Regarding the situation in Italy, where the case study described in this article was developed: of note, following the conversion of the law decree of May 19, 2020 into law, the Specialty School in Medicine and palliative care has been created (https://www.gazzettaufficiale.it/eli/gu/2020/08/31/216/sg/pdf), beginning in the academic year 2021–2022 (84). A more structured and comprehensive training of professionals in palliative care will hopefully facilitate the adoption and optimal implementation of the model. A clear training pathway as dual board-certified medical hematologist/oncologist and (early) palliative care physician is worth pursuing, in order to avoid hematologists and oncologists still confusing palliative care with end-of-life care (85, 86).

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

All authors contributed to conception and design, bibliography review and data analysis and interpretation, manuscript writing, and final approval of manuscript.

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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

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First-line Immuno-chemotherapy for extensive-stage small-cell lung cancer: A network meta-analysis and cost-effectiveness analysis

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Introduction: Many randomized controlled trials have indicated that immuno-chemotherapy could generate clinical benefits, though the cost of immuno-chemotherapy was so prohibitive and the options were varied. This investigation aimed at evaluating effectiveness, safety, and cost-effectiveness for immuno-chemotherapy as a first-line therapeutic option for ES-SCLC patients.

Methods: Multiple scientific literature repositories were searched for clinical studies where immuno-chemotherapy was regarded as the first-line treatment for ES-SCLC, which were published in English between Jan 1, 2000, and Nov 30, 2021. This study conducted a network meta-analysis (NMA) and cost-effectiveness analysis (CEA) based upon US-resident payer perspectives. Overall survival (OS), progression-free survival (PFS), and adverse events (AEs) were evaluated through NMA. In addition, costings, life-years (LYs), quality-adjusted life-years (QALYs), and incremental cost–benefit ratio (ICER) were estimated by CEA.

Results: We identified 200 relevant search records, of which four randomized controlled trials (RCTs) (2,793 patients) were included. NMA demonstrated that the effect of atezolizumab plus chemotherapy was ranked at a more elevated position in comparison to other immuno-chemotherapy options and chemotherapy alone, within the general population. The influence of atezolizumab plus chemotherapy and durvalumab plus chemotherapy was ranked higher within populations experiencing non-brain metastases (NBMs) andbrain metastases (BMs), respectively. The CEA revealed that the ICERs of immuno-chemotherapy over chemotherapyalone were higher than the willingness-to-pay (WTP) threshold of $150,000/QALY in any population. However, treatment with atezolizumab plus chemotherapy and durvalumab plus chemotherapy were more favorable health advantages than other immuno-chemotherapy regimens and chemotherapy alone, and the results were 1.02 QALYs and 0.89 QALYs within overall populations and populations with BMs, respectively.

Conclusion: The NMA and cost-effectiveness investigation demonstrated that atezolizumab plus chemotherapy could be an optimal first-line therapeutic option for ES-SCLC when compared with other immuno-chemotherapy regimens. Durvalumab plus chemotherapy is likely to be the most favorable first-line therapeutic option for ES-SCLC with BMs.

KEYWORDS

extensive-stage small-cell lung cancer, immuno-chemotherapy, network meta-analysis, cost-effectiveness, quality-adjusted life-years

1. Introduction

Lung cancer has the second-highest morbidity and highest mortalityamong all cancer models globally, with over 2.2 million and 230,000 cases diagnosed, and over 1.79 million and 130,000 deaths occurring globally and within the United States (US) in 2021, respectively (1, 2). Small cell lung cancer accounted for more than 10% of lung cancer, and up to 60% were diagnosed as extensive-stage small cell lung cancer (ES-SCLC), with a 5-year survival rate of only 2% (3–5). The most common distant metastases were brain metastases (BMs), which are prevalent within 10% of such clinical cases at initial diagnosis, accounting for more than 50% incidence within 2 years (6).

During the past 30 years, etoposide plus platinum (EP) was established as a first-line chemotherapeutic option for ES-SCLC, though the survival of patients has not improved significantly, and patients typically endure recurrence within 1–2 years. A phase III clinical data of ES-SCLC demonstrated that the survival time of the chemotherapeutics group increased by only 0.63 days per year (7). Therefore, it is necessary and urgent to develop new drugs to treat ES-SCLC.

The wide use of immune checkpoint inhibitors (ICIs) has paved the road for a novel age of oncology therapeutics, which could block the programmed cell death 1 (PD-1), programmed death-ligand 1(PD-L1), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) signaling pathways, and are becoming a novel treatment for ES-SCLC since such schemes could enhance survival rate and quality-of-life. For example, the IMpower133 study demonstrated that adding atezolizumab (PD-L1) to chemotherapy for first-line treatment of ES-SCLC resulted in significant improvement in overall survival (OS, hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.60 to 0.95; $p = 0.0154$) and progression-free survival (PFS, HR, 0.77; 95% CI, 0.62 to 0.96; $p = 0.02$) versus chemotherapy (8, 9). The CASPIAN study showed that it sustained enhanced OS benefit (HR, 0.75; 95% CI, 0.62 to 0.91; $p = 0.0032$) while it did not prolong PFS (HR, 0.84; 95% CI, 0.70 to 1.01) through introducing durvalumab combined with chemotherapeutics for ES-SCLC clinical cases in comparison to chemotherapy alone, though durvalumab plus tremelimumab within chemotherapeutics did not significantly improve OS (HR, 0.82; 95% CI, 0.68 to 1.00; $p = 0.045$) and PFS (HR 0.84, 95% CI 0.70 to 1.01) (10). The KEYNOTE-604 study illustrated that pembrolizumab plus chemotherapy significantly improved PFS (HR, 0.75; 95% CI, 0.61 to 0.91; $p = 0.0023$) and slightly prolonged OS (HR, 0.78; 95% CI, 0.63 to 0.97; $p = 0.0164$) compared with chemotherapy as initial therapy for ES-SCLC cases (11). The CA184-156 investigation revealed that ipilimumab plus chemotherapy failed to extend OS (HR, 0.94; 95% CI, 0.81 to 1.09; $p = 0.3775$) and slightly extend PFS (HR, 0.85; 95% CI, 0.75 to 0.97; $p = 0.0161$) versus chemotherapy alone within clinical cases having novel-diagnosed ES-SCLC (12). Founded upon such datasets, atezolizumab or durvalumab were approved by the US Food and Drug Administration (FDA) (13, 14) and the National Comprehensive Cancer Network (NCCN) for combination therapy with EP as a first-line option against ES-SCLC (15).

However, considering that there is no research to directly compare different immuno-chemotherapy regimens, it is not clear which therapeutic option must be recommended as initial treatment in such clinical cases. Based upon present healthcare scenarios and relevant stakeholders, we need more proof to validate different immuno-chemotherapy within oncology health care to provide effective medical leverage with decent costings. Consequently, this investigation employed recently reported randomized controlled trials (RCTs) for network meta-analysis (NMA) and cost-effectiveness analysis (CEA) for evaluating effectiveness, safety, and cost-effectiveness for immuno-chemotherapy and chemotherapy alone as the initial therapeutic option for ES-SCLC clinical cases, from a US payer perspective.

2. Methods

This work was guided by the PRISMA statement, which included a PRISMA NMA checklist and the consolidated health economic evaluation reporting standards statement (CHEERS) checklist (Supplementary Tables 2, 3 within the Supplementary material).

2.1. Search strategy and inclusion criteria

A systematic review and NMA were conducted for identifying eligible phase III RCTs to compare regimens containing ICIs plus chemotherapy in first-line treatment. We retrieved the Pubmed, Embase, Cochrane, and Web of Science databases for published articles written in English from Jan 1, 2000, to Nov 30, 2021, with the search terms "PD-1," "PD-L1," "immunotherapy," "chemotherapy," "extensive-stage small-cell lung cancer," and "clinical trial" (Supplementary Table 1 in the Supplementary material). In addition, the investigation also focused on abstracts reported by the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO). Finally, relevant literature was manually screened to avoid missing articles.

Inclusion criteria: (1) patients diagnosed with ES-SCLC; (2) articles in which participants received both types of treatment, one of which was immuno-chemotherapy and the other was chemotherapy; (3) both treatment measures were in the initial treatment environment of ES-SCLC patients; (4) phase III RCTs; (5) the article had the most complete and updated data of the trial; (6) studies published in English. Studies not matching the inclusion criteria were excluded. YWZ and KL carried out literature retrieval and data extraction independently. Whenever duplicate studies were identified, the article having the most comprehensive and recent investigation data were included. Reviews / systematic reviews, meta-analyses, and CEAs were excluded from this investigation.

2.2. Data extraction and determination of bias risks

Details were extracted from identified articles, such as author, publication year, trial name or identification, treatment regimens of experimental groups and control groups, number of patients treated, HR of OS and PFS of the overall population, median OS and PFS, together with the incidence of grade 3/4 AEs from each included investigation. Additionally, the odds ratio (OR) of grade 3/4 AEs and the HR of OS and PFS of the population with BMs or non-brain metastases (NBMs) were extracted.

Individual RCT article bias risks were evaluated in line with the Cochrane Collaboration guideline (16), valuating multiple facets for RCT experimental designs, behavior, and detail

descriptions. Seven tools were used to assess individual RCT results, namely: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias.

2.3. Statistical analysis

R software (version 4.1.1)[1] with the package "netmeta" was employed for comparative analysis. We combined the HR and 95% CI that was collected. However, since just one RCT informed individual pair-wise comparisons, with paucity in datasets for evaluating heterogeneity across trials, a fixed-effect model was established. Consequently, the frequency method was employed for comparing effectiveness and safety for different schemes. The HR of OS and PFS, corresponding 95% CI, *p*-value, and OR of AEs were calculated. Subgroup analyses were performed on status with or without BMs. Finally, according to the obtained 95% Cl of HR and p-value, the best treatment schemes were sorted.

2.4. Cost-effectiveness analysis

2.4.1. Model structure

A Markov model and decision tree having multiple health-parameters (PFS, progressive disease (PD), and death) (Supplementary Figure 5 in the Supplementary material) was established to assess costings and efficacy for different initial patient treatments for ES-SCLC. The Markov model cycle was determined to be 6 weeks based on the patient's survival and dosing follow-up protocol. Since tremelimumab has not obtained obvious clinical benefits and was not listed, the decision trees included 5 initial therapeutic options: (1) atezolizumab plus chemotherapy, (2) durvalumab plus chemotherapy, (3) pembrolizumab plus chemotherapy, (4) ipilimumab plus chemotherapy, and (5) chemotherapy. Over time, the patient's health status deteriorated and led to mortality, with more than 99% of the registered patients dead over the last 15 years. All patients started PFS status and could receive five kinds of initial treatment strategies randomly. Upon PD or unacceptable toxicity and AEs, some patients received topotecan as subsequent treatment, according to Koichi Goto's recommendations (17); Other patients received supportive treatment (15). To better reflect the current clinical work, the study considered that patients received palliative treatment before the mortality event. All doses and dosing schedules for each treatment regimen were collected from corresponding RCTs (9–12) (Supplementary Table 5 in the Supplementary material).

The study adopted costings and influence from a 3% discounted rate per year (18). The outputs encompassed overall cost, life-years (LYs), quality-adjusted LYs (QALYs), and incremental cost-effectiveness ratios (ICERs). The study also focused on population CEA with or without BMs. Depending upon the U.S. consumer-price index, all costings related to healthcare services were inflated to the value of 2021, and willingness-to-pay (WTP) in the United States was $150,000 (19, 20). The Markov model used TreeAge Pro 2020® (TreeAge Software™, Williamstown, MA)[2].

2.4.2. Model survival and progression risk estimates

This research implemented GetData Graph Digitizer® (version 2.26)[3] for gathering data from OS and PFS curve-strategy from RCTs. Consequently, we reconstructed the OS and PFS curves of chemotherapeutics patients depending upon Kaplan–Meier (KM) chemotherapeutic curves of four RCTs and such data were consequently employed for fitting parametric survival models. Peak-consistent Weibull distribution was chosen depending upon Akaike's information criterion (AIC) and Bayesian information criterion (BIC) (Supplementary Table 6; Supplementary Figures 6, 7 in the Supplementary material) (21). Consequently, the study used Weibull distribution and obtained two-parameter, shape (γ) and scale (λ), which were determined through such a fit. This study employed Hoyle and Henley's suggested methodology (22) (Table 1).

Time-dependency transition probabilities(tp) are vital for such modeling evaluations. Tp for individual Markov cycles was determined depending upon following formula: $tp(t_u) = 1 - \exp\left\{\lambda(t-u)^{\gamma} - \lambda t^{\gamma}\right\}(\lambda > 0, \gamma > 0)$ (26).

where Markov cycle = u, arrival at state t after u Markov cycles i = tu, respectively.

2.4.3. Cost and utility estimates

This study considered just immediate medical expenses from a US payer perspective, including drug costs (24), AEs costs (with the assumption that AEs occurred within just 1 cycle during PFS and PD states) (20, 23, 25, 27), administration, tumor imaging, laboratory (23), and death associated costs (25), and best supportive care (28).

Based on four RCTs and clinical practice, carboplatin was selected as the main treatment regimen in the chemotherapeutics group. Once drug cost per cycle was determined, assuming the patient was male-gender, 65 years old, weighing 70 Kg, the height of 170, and body-surface-area 1.84m^2, area-under-concentration (AUC) curve of 5 mg/ml/min, together with presumed serum creatinine being 1 (29). Medical monitoring costings encompassed financial charges for computed tomography or magnetic resonance imaging (at six-week intervals for the initial 48 weeks and 9-week intervals afterward) (9, 11). This study solely added costings for managing grade 3/4 AEs (frequency > 5%) within this model that had distinctly varying probabilities across RCT arms. The entirety of costings linked to healthcare provisions was inflated to correspondent values in 2021, depending upon the US consumer-price index (Table 1).

We used previously published utilities of 0.673 and 0.473 (25) as the mean health utility value for PFS and PD states, accordingly. This investigation also included dis-utility values of grade 3/4 AEs within analysis (23, 25, 27).

1 http://www.r-project.org

2 https://www.treeage.com

3 http://www.getdata-graph-digitizer.com/index.php

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TABLE 1 Model parameters: baseline values, ranges, and distributions for sensitivity analysis.

Parameters	Baseline value	Range		References	Distribution
		Minimum	Maximum		
Survival					
Weibull survival model of OS of C	Scale = 0.010872,	–	–	(7–11)	–
	Shape = 1.750803				
Weibull survival model of PFS of C	Scale = 0.026945,	–	–		–
	Shape = 2.100966				
Weibull survival model of OS of AC	Scale = 0.01412,	–	–	(7, 8)	–
	Shape = 1.490903				
Weibull survival model of PFS of AC	Scale = 0.11144,		-		-
	Shape = 1.19819	–			
Weibull survival model of OS of DC	Scale = 0.022259,	–	–	(9)	–
	Shape = 1.334609				
Weibull survival model of PFS of DC	Scale = 0.15276,	–	–		-
	Shape = 0.92421				
Weibull survival model of OS of PC	Scale = 0.03787,	–	–	(10)	–
	Shape = 1.1735				
Weibull survival model of PFS of PC	Scale = 0.07424,	–	–		-
	Shape = 1.40271				
Weibull survival model of OS of IC	Scale = 0.008878,	–	–	(11)	–
	Shape = 1.790279				
Weibull survival model of PFS of IC	Scale = 0.02302	–	–		-
	Shape = 2.11942				
Risk for main AEs in C group					
Risk of neutropenia	0.29	0.23	0.35	(7–11)	Beta
Risk of anemia	0.12	0.10	0.15	(7–11)	Beta
Risk of thrombocytopenia	0.07	0.06	0.09	(7–11)	Beta
Risk of leucopenia	0.05	0.04	0.06	(7–11)	Beta
Risk of neutrophil count decreased	0.07	0.05	0.08	(7–11)	Beta
Risk for main AEs in AC group					
Risk of thrombocytopenia	0.10	0.08	0.12	(7)	Beta
Risk of neutropenia	0.23	0.18	0.27	(7)	Beta
Risk of anemia	0.14	0.11	0.17	(7)	Beta
Risk of neutrophil count decreased	0.14	0.11	0.17	(7)	Beta
Risk of leucopenia	0.05	0.04	0.06	(7)	Beta
Risk for main AEs in DC group					
Risk of neutropenia	0.24	0.19	0.29	(9)	Beta
Risk of anemia	0.09	0.07	0.11	(9)	Beta
Risk of thrombocytopenia	0.06	0.05	0.07	(9)	Beta
Risk of leucopenia	0.06	0.05	0.07	(9)	Beta
Risk of neutrophil count decreased	0.06	0.05	0.07	(9)	Beta
Risk of febrile neutropenia	0.06	0.05	0.07	(9)	Beta
Risk of hyponatraemia	0.06	0.05	0.07	(9)	Beta
Risk for main AEs in PC group					

(Continued)

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TABLE 1 (Continued)

Parameters	Baseline value	Range		References	Distribution
		Minimum	Maximum		
Risk of neutropenia	0.44	0.35	0.52	(10)	Beta
Risk of anemia	0.16	0.13	0.19	(10)	Beta
Risk of thrombocytopenia	0.14	0.11	0.17	(10)	Beta
Risk of leucopenia	0.12	0.09	0.14	(10)	Beta
Risk of pneumonia	0.07	0.05	0.08	(10)	Beta
Risk for main AEs in IC group					
Risk of diarrhea	0.07	0.06	0.08	(11)	Beta
Risk of anemia	0.08	0.06	0.10	(11)	Beta
Risk of neutropenia	0.14	0.11	0.17	(11)	Beta
Risk of neutrophil count decreased	0.07	0.06	0.08	(11)	Beta
Utility					
Utility PFS in first-line treatment	0.673	0.54	0.81	(23)	Beta
Utility PD	0.473	0.38	0.57	(23, 24)	Beta
Disutility due to AEs					
Neutropenia	0.09	0.07	0.11	(24)	Beta
Anemia	0.073	0.06	0.09	(24)	Beta
Leucopenia	0.09	0.07	0.11	(24)	Beta
Pneumonia	0.09	0.07	0.11	(25)	Beta
Thrombocytopenia	0.65	0.52	0.78	(24)	Beta
Neutrophil count decreased	0.09	0.07	0.11	(24)	Beta
Febrile Neutropenia	0.09	0.07	0.11	(24)	Beta
Hyponatraemia	0.094	0.08	0.11	(23)	Beta
Diarrhea	0.22	0.18	0.26	(23)	Beta
AEs disutility for AC	0.09	0.07	0.11	(23)	Beta
AEs disutility for DC	0.094	0.08	0.11	(23)	Beta
Drug cost, $/per cycle					
Atezolizumab	19,140	15,312	22,968	(26)	Gamma
Durvaluma	23,059	18,447	27,671	(26)	Gamma
Pembrolizumab	21,102	16,881	25,322	(26)	Gamma
Ipilimumab	222,107	177,686	266,539	(26)	Gamma
Etoposide	88	70	105	(26)	Gamma
Carboplatin	52	41	62	(26)	Gamma
Topotecan	141	113	169	(26)	Gamma
Cost of AEs, $					
Chemotherapy	15,168	12,134	18,202	(20, 23, 25, 27)	Gamma
Atezolizumab plus chemotherapy	15,866	12,693	19,039	(20, 23, 25, 27)	Gamma
Durvaluma plus chemotherapy	15,499	12,399	18,599	(20, 23, 25, 27)	Gamma
Pembrolizumab plus chemotherapy	20,581	16,465	24,697	(20, 23, 25, 27)	Gamma
Ipilimumab plus chemotherapy	8,536	6,829	10,243	(20, 23, 25, 27)	Gamma
Laboratory per cycle	315	252	378	(22)	Gamma
Tumor imaging per cycle	231	185	277	(24)	Gamma
Administration per cycle	140	112	168	(24)	Gamma

(Continued)

TABLE 1 (Continued)

Parameters	Baseline value	Range		References	Distribution
		Minimum	Maximum		
Best supportive care per cycle	3,299	2,639	3,959	(27)	Gamma
Death associated costs per patient	9,433	7,546	11,320	(23)	Gamma
Discount rate	0.03	–	–	(17)	–

OS, overall survival; PFS, progression-free survival; C; chemotherapy; AC; atezolizumab plus chemotherapy; DC; durvaluma plus chemotherapy; PC; pembrolizumab plus chemotherapy; IC; ipilimumab plus chemotherapy; AEs, adverse events.

2.4.4. Sensitivity and scenario analysis

This investigation employed serial sensitivity evaluating predictions for modeling outcome uncertainties. One-way sensitivity evaluation was performed within a variance of 20% baseline values, depending upon varying values for a specific parameter (within the expected range) and pre-determined methodologies for examining individual parameter-driven influences over ICERs (23). This investigation additionally conducted probabilistic sensitivity analyses for evaluating the probability of efficacy by therapeutic regimens through 10,000 Monte Carlo repetitions. A cost-effectiveness adequacy curve for individual therapeutic modalities was assessed to present probabilities of cost-effectiveness.

Subgroup analyses were performed on status with or without BMs of four RCTs. Due to insufficient data for several RCTs, this investigation used identical pooled chemotherapeutics KM to obtain depending upon subgroup-defined HRs, as described by Hoyle (30) for lack of OS and PFS curves regarding BMs status of subgroups.

In addition, we conducted a scenario analysis, where ICIs maintenance phase until death after 4 cycles of first-line treatment, for evaluating if maintenance time for ICIs had a major influence on this investigation's outcomes.

3. Results

3.1. Included studies

We searched 200 records, and 63 eligible articles were searched in full text. After screening, four cluster RCTs, involving 2,793 patients, were included (Supplementary Table 4; Supplementary Figure 1 in the Supplementary material). These patients received first-line treatment with atezolizumab plus chemotherapy ($n = 201$ patients), durvalumab plus chemotherapy ($n = 268$ patients), durvalumab with tremelimumab plus chemotherapy ($n = 268$ patients), pembrolizumab plus chemotherapy (n = 228 patients), ipilimumab plus chemotherapy ($n = 478$ patients), and chemotherapy (n = 1,172 patients).

3.2. Risk-bias proof evaluations

We employed RevMan® (version 5.4) to summarize risk-bias (Supplementary Figure 2 in the Supplementary material). Two studies were designated as cluster RCTs and employed randomization concealment. Three investigations were described as double-blinded. Three investigations were found to have reduced risk-bias due to blinding of outcome evaluation, while all studies were judged to have a low risk of bias for incomplete outcome data and selective reporting.

3.3. Results of the network meta-analysis

The network plots were built using R software (version 4.1.1), including five immuno-chemotherapy regimens (atezolizumab plus chemotherapy, durvalumab plus chemotherapy, durvalumab with tremelimumab plus chemotherapy, pembrolizumab plus chemotherapy, and ipilimumab plus chemotherapy) and one control regimen (chemotherapy) (Supplementary Figure 3 in the Supplementary material). Indirect comparison showed that atezolizumab plus chemotherapy (HR, 0.76; 95% CI, 0.60 to 0.96 and HR, 1.32; 95% CI, 1.05 to 1.66), durvalumab plus chemotherapy (HR, 0.75; 95% CI, 0.62 to 0.91 and HR, 1.33; 95% CI, 0.62 to 0.91), durvalumab with tremelimumab plus chemotherapy (HR, 0.82; 95% CI, 0.68 to 0.99 and HR, 1.23; 95% CI, 1.01 to 1.48), and pembrolizumab plus chemotherapy (HR, 0.80; 95% CI, 0.65 to 0.99 and HR, 1.25; 95% CI, 1.01 to 1.55) had significant statistical improvement compared with chemotherapy in OS, and atezolizumab plus chemotherapy (HR, 0.77; 95% CI, 0.63 to 0.95 and HR, 1.30; 95% CI, 1.06 to 1.60), durvalumab plus chemotherapy (HR, 0.80; 95% CI, 0.66 to 0.97 and HR, 1.25; 95% CI, 0.66 to 0.97), pembrolizumab plus chemotherapy (HR, 0.75; 95% CI, 0.61 to 0.92 and HR, 1.33; 95% CI, 0.61 to 0.92), and ipilimumab plus chemotherapy (HR, 0.85; 95% CI, 0.75 to 0.97 and HR, 1.18; 95% CI, 0.75 to 0.97) had significant statistical improvement compared with chemotherapy in PFS in the overall population. No statistically significant differences in PFS and OS were found between the five immuno-chemotherapy regimens. In the population with BMs, durvalumab plus chemotherapy (HR, 0.76; 95% CI, 0.62 to 0.93 and HR, 1.32; 95% CI, 1.08 to 1.60) and ipilimumab plus chemotherapy (HR, 0.63; 95% CI, 0.41 to 0.98 and HR, 1.58; 95% CI, 1.02 to 2.44) were significantly improved in OS and PFS in comparison to chemotherapy. In the population with NBMs, atezolizumab plus chemotherapy (HR, 0.74; 95% CI, 0.58 to 0.94 and HR, 1.35; 95% CI, 1.06 to 1.72), durvalumab with tremelimumab plus chemotherapy (HR, 0.81; 95% CI, 0.67 to 0.99 and HR, 1.24; 95% CI, 1.06 to 1.72), pembrolizumab plus chemotherapy (HR, 0.75; 95% CI, 0.60 to 0.94 and HR, 1.33; 95% CI, 1.07 to 1.67); atezolizumab plus chemotherapy (HR, 0.75; 95% CI, 0.60 to 0.93 and HR, 1.33; 95% CI, 1.07 to 1.66), durvalumab plus chemotherapy (HR, 0.80; 95% CI, 0.66 to 0.97 and HR, 1.25; 95% CI, 1.04 to 1.51), pembrolizumab plus chemotherapy (HR, 0.69; 95% CI, 1.04 to 1.51 and HR, 1.45; 95% CI, 1.17 to 1.80), and ipilimumab plus chemotherapy (HR, 0.85; 95% CI, 0.78 to 0.97 and HR, 1.18; 95% CI, 1.04 to 1.34) were significantly improved in PFS compared with chemotherapy.

The best treatment results were ranked according to *value of p* (individual outcomes), where raised values were more successful. Among the overall populations, the regimen having peak *value of p* for OS was durvalumab plus chemotherapy ($p = 0.78$), followed by

atezolizumab plus chemotherapy ($p = 0.74$). However, the regimen with the highest *value of p* for PFS was pembrolizumab plus chemotherapy ($p = 0.78$), followed by atezolizumab plus chemotherapy ($p = 0.71$), durvalumab plus chemotherapy ($p = 0.61$). The regimens with the highest *value of p* for OS and PFS in the population with NBMs were durvalumab plus chemotherapy ($p = 0.88$ and $p = 0.77$). Among the population with BMs, the regimen with the highest *value of p* for OS and PFS were atezolizumab plus chemotherapy ($p = 0.76$) and pembrolizumab plus chemotherapy ($p = 0.88$), respectively. The results of indirect comparisons and the *p*-values of the PFS and OS of each regimen were shown in Figures 1, 2, respectively.

The safety table and forest plot showed that the five immuno-chemotherapy schemes have considerable safety profiles for any grade AEs (Supplementary Figure 4; Supplementary Table 7 in the Supplementary material). The general safety of immuno-chemotherapy ranked from high to low for all AEs was as follows: chemotherapy (probability 90%), ipilimumab plus chemotherapy (56%), atezolizumab plus chemotherapy (52%), durvalumab plus chemotherapy (52%), pembrolizumab plus chemotherapy (37%), and durvalumab with tremelimumab plus chemotherapy (13%). The general safety of immuno-chemotherapy ranked from high to low for severe AEs was as follows: chemotherapy (70%), atezolizumab plus chemotherapy (63%), durvalumab plus chemotherapy (57%), pembrolizumab plus chemotherapy (43%), ipilimumab plus chemotherapy (38%), and durvalumab with tremelimumab plus chemotherapy (31%).

3.4. Results of the cost-effectiveness analyses

Regarding ES-SCLC cases, this investigation expressed the output effects of five interventions by QALYs (LYs), from more to less was as follows: atezolizumab plus chemotherapy (1.02 QALYs and 1.91 LYs), durvalumab plus chemotherapy (1.01 QALYs and 1.90 LYs), pembrolizumab plus chemotherapy (0.93 QALYs and 1.80 LYs), ipilimumab plus chemotherapy (0.85 QALYs and 1.55 LYs), and chemotherapy (0.77 QALYs and 1.44 LYs). The least total cost of each treatment regimen was ranked from high to low as follows: the total cost of ipilimumab plus chemotherapy was the highest, which was $568,657, followed by pembrolizumab plus chemotherapy ($241,682), durvalumab plus chemotherapy ($229,620), and atezolizumab plus chemotherapy ($213,988). The lowest total cost of chemotherapy was $133,625. Post-further analysis, atezolizumab plus chemotherapy, durvalumab plus chemotherapy, pembrolizumab plus chemotherapy, ipilimumab plus chemotherapy obtained an ICER of $321,452/QALY, $399,978/QALY, $675,358/QALY, and $5,437,894/QALY, respectively, compared with chemotherapy. The baseline results and pairwise comparison of ICER were shown in Table 2; Supplementary Table 8.

The one-way sensitivity analysis showed it was highly sensitive for the utility of PD against chemotherapy. Other considerable influences were the risk of neutropenia in the chemotherapy group or immuno-chemotherapy group, cost of ICIs, and utility of PD. Alternative factors encompassed within sensitivity analysis, such as the costing and disutilities of AEs, had a minimal impact on ICER (Supplementary Figure 8 in the Supplementary material).

Dataset outcomes for acceptability curves (Figure 3) and ICER scatterplot (Supplementary Figure 9 in the Supplementary material) demonstrated that the probability of atezolizumab plus chemotherapy, durvalumab plus chemotherapy, pembrolizumab plus chemotherapy, and ipilimumab plus chemotherapy being cost-effective were 32, 29 10, 0% in the overall population, respectively, compared with that of chemotherapy a WTP threshold of $150,000.

Regarding patient-populations experiencing BMs and NBMs, ICERs for atezolizumab plus chemotherapy, durvalumab plus chemotherapy, pembrolizumab plus chemotherapy, ipilimumab plus chemotherapy versus chemotherapy were $5,437,894 and $429,606, $621,350 and $718,640, $-446,292, and $1,272,538, and $-3,203,067 and $20,322,400 per QALY, respectively (Table 2). Results of ICER scatterplot (Supplementary Figures 10, 11 in the Supplementary material) showed that the probability of atezolizumab plus chemotherapy, durvalumab plus chemotherapy, pembrolizumab plus chemotherapy, and ipilimumab plus chemotherapy being cost-effective were 12 and 34%, 39 and 20%, 0 and 19%, 0 and 0% in the population with BMs and NBMs, compared with that of chemotherapy a WTP threshold of $150,000, respectively.

Scenario-analysis outcomes suggested that ICIs maintenance therapy resulted in the health costings linked to initial treatment increasing drastically, though this investigation's outcome was not altered. This investigation assumed that clinical cases had ICIs maintenance therapy until death after 4 cycles of initial treatment, whereby health costs of the first-line atezolizumab plus chemotherapy, durvalumab plus chemotherapy, pembrolizumab plus chemotherapy, and ipilimumab plus chemotherapy were $279,513, $326,911, $306,097, and $1,271,747, respectively. An the ICERs were $355,700, $519,417, $731,140, and $5,963,788 per QALY, respectively.

4. Discussion

Recently, the promotion of ICIs has vastly shifted therapeutic options for ES-SCLC patients. Some encouraging results of phase III clinical studies demonstrated that introducing atezolizumab, durvalumab, durvalumab plus tremelimumab, pembrolizumab, and ipilimumab to chemotherapy shows clinical activity. Considering that these expensive drugs have brought a heavy burden on social health resources and patients, it is unclear which treatment regimen has the best efficacy and safety in the first-line treatment of ES-SCLC. Consequently, this investigation pioneered a comprehensive comparative clinical trial of immuno-chemotherapy and proved that one of the ICIs has better efficacy, safety, and overall economic outcomes. The results of NMAs indicated that atezolizumab plus chemotherapy and durvalumab plus chemotherapy regimens produced more survival benefits in patients with NBMs and BMs than other immuno-chemotherapy regimens and chemotherapy, respectively. Furthermore, the survival advantages of atezolizumab plus chemotherapy and durvalumab plus chemotherapy translated into the highest QALYs in patients with NBMs and BMs, respectively. All five immuno-chemotherapy regimens were associated with all levels of AEs risk, and ipilimumab plus chemotherapy strategy was linked to lowered risk for all-grade AEs (all levels) in comparison to chemotherapy. Unexpectedly, the safety of immuno-chemotherapy regimens is lower than that of chemotherapy strategy, which could be due to the combined regimens summarize AEs of ICIs and chemotherapy. Consequently, this assessment reflects the universal profiles of the current research results.

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A. Overall population

AC	1.01 (0.75 to 1.37)	0.93 (0.69 to 1.25)	0.95 (0.70 to 1.30)	0.81 (0.62 to 1.06)	**0.76 (0.60 to 0.96)**	0.74
0.99 (0.73 to 1.33)	**DC**	0.92 (0.70 to 1.20)	0.94 (0.70 to 1.25)	0.80 (0.63 to 1.02)	**0.75 (0.62 to 0.91)**	0.78
1.08 (0.80 to 1.46)	1.09 (0.83 to 1.44)	**DTC**	1.03 (0.77 to 1.37)	0.87 (0.68 to 1.11)	**0.82 (0.68 to 0.99)**	0.57
1.05 (0.77 to 1.44)	1.07 (0.80 to 1.42)	0.98 (0.73 to 1.30)	**PC**	0.85 (0.66 to 1.10)	**0.80 (0.65 to 0.99)**	0.63
1.24 (0.94 to 1.63)	1.25 (0.98 to1.60)	1.15 (0.90 to 1.46)	1.18 (0.91 to 1.52)	**IC**	0.94 (0.81 to 1.09)	0.23
1.32 (1.05 to 1.66)	**1.33 (1.10 to 1.61)**	**1.23 (1.01 to 1.48)**	**1.25 (1.01 to 1.55)**	1.06 (0.91 to 1.23)	**C**	0.05
0.74	0.78	0.57	0.63	0.23	0.05	**P-Score**

B. Population with brain metastases

AC	1.26 (0.59 to 2.71)	1.06 (0.42 to 2.65)	0.72 (0.28 to 1.89)	0.61 (0.26 to 1.43)	0.96 (0.46 to 2.01)	0.58
0.79 (0.37 to 1.70)	**DC**	0.84 (0.47 to 1.50)	0.58 (0.30 to 1.09)	**0.48 (0.30 to 0.78)**	**0.76 (0.62 to 0.93)**	0.88
0.95 (0.38 to 2.38)	1.20 (0.67 to 2.15)	**DTC**	0.84 (0.47 to 1.50)	0.58 (0.30 to 1.09)	**0.48 (0.30 to 0.78)**	0.64
1.38 (0.53 to 3.57)	1.74 (0.92 to 3.29)	1.45 (0.64 to 3.29)	**PC**	0.84 (0.40 to 1.76)	1.32 (0.72 to 2.42)	0.27
1.65 (0.70 to 3.88)	**2.08 (1.29 to 3.36)**	1.74 (0.86 to 3.50)	1.20 (0.57 to 2.53)	**IC**	**1.58 (1.02 to 2.44)**	0.11
1.04 (0.50 to 2.18)	**1.32 (1.08 to 1.60)**	1.10 (0.64 to 1.90)	0.76 (0.41 to 1.39)	**0.63 (0.41 to 0.98)**	**C**	0.53
0.58	0.88	0.64	0.27	0.11	0.53	**P-Score**

C. Population with non-brain metastases

AC	0.94 (0.50 to 1.76)	0.91 (0.67 to 1.25)	0.99 (0.71 to 1.37)	**0.72 (0.54 to 0.96)**	**0.74 (0.58 to 0.94)**	0.76
1.07 (0.57 to 2.01)	**DC**	0.98 (0.53 to 1.80)	1.05 (0.56 to 1.97)	0.79 (0.61 to 1.01)	1.07 (0.57 to 2.00)	0.59
1.10 (0.80 to 1.50)	1.03 (0.55 to 1.90)	**DTC**	0.98 (0.53 to 1.80)	1.05 (0.56 to 1.97)	0.79 (0.61 to 1.01)	0.60
1.01 (0.73 to 1.41)	0.95 (0.51 to 1.77)	0.93 (0.69 to 1.25)	**PC**	**0.73 (0.55 to 0.96)**	**0.75 (0.60 to 0.94)**	0.74
1.39 (1.05 to 1.86)	1.30 (0.71 to 2.38)	1.27 (0.99 to 1.64)	**1.37 (1.05 to 1.80)**	**IC**	1.03 (0.88 to 1.20)	0.12
1.35 (1.06 to 1.72)	1.27 (0.71 to 2.27)	**1.24 (1.01 to 1.50)**	**1.33 (1.07 to 1.67)**	0.97 (0.83 to 1.13)	**C**	0.18
0.76	0.59	0.60	0.74	0.12	0.18	**P-Score**

FIGURE 1
Hazard ratios (gray and brown cell) and *p*-values (blue cell) of the network meta-analysis of the overall survival in the overall population **(A)**, population with brain metastases **(B)**, and population with non-brain metastases **(C)**. AC, atezolizumab plus chemotherapy; DC, durvaluma plus chemotherapy; DTC, durvalumab with tremelimumab plus chemotherapy; PC, pembrolizumab plus chemotherapy; IC, ipilimumab plus chemotherapy; C, chemotherapy.

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A. Overall population

AC	0.96 (0.73 to 1.27)	0.92 (0.70 to 1.21)	1.03 (0.77 to 1.37)	0.91 (0.71 to 1.15)	**0.77 (0.63 to 0.95)**	0.71
1.04 (0.79 to 1.37)	**DC**	0.95 (0.73 to 1.24)	1.07 (0.81 to 1.40)	0.94 (0.75 to 1.18)	**0.80 (0.66 to 0.97)**	0.61
1.09 (0.83 to 1.44)	1.05 (0.81 to 1.37)	**DTC**	1.12 (0.85 to 1.47)	0.99 (0.79 to 1.24)	0.84 (0.70 to 1.01)	0.47
0.97 (0.73 to 1.30)	0.94 (0.71 to 1.23)	0.89 (0.68 to 1.17)	**PC**	0.88 (0.70 to 1.12)	**0.75 (0.61 to 0.92)**	0.78
1.10 (0.87 to 1.41)	1.06 (0.85 to 1.33)	1.01 (0.81 to 1.27)	1.13 (0.89 to 1.44)	**IC**	**0.85 (0.75 to 0.97)**	0.42
1.30 (1.06 to 1.60)	**1.25 (1.04 to 1.51)**	1.19 (0.99 to 1.43)	**1.33 (1.09 to 1.63)**	**1.18 (1.04 to 1.34)**	**C**	0.01
0.71	0.61	0.47	0.78	0.42	0.01	**P-Score**

B. Population with brain metastases

AC	1.23 (0.59 to 2.54)	1.17 (0.56 to 2.41)	0.92 (0.37 to 2.28)	1.15 (0.56 to 2.36)	0.98 (0.49 to 1.98)	0.42
0.82 (0.39 to 1.69)	**DC**	0.95 (0.73 to 1.24)	0.75 (0.41 to 1.37)	0.94 (0.75 to 1.18)	**0.80 (0.66 to 0.97)**	0.77
0.86 (0.41 to 1.77)	1.05 (0.81 to 1.37)	**DTC**	0.79 (0.43 to 1.44)	0.99 (0.79 to 1.24)	0.84 (0.70 to 1.01)	0.66
1.09 (0.44 to 2.72)	1.34 (0.73 to 2.46)	1.27 (0.69 to 2.34)	**PC**	1.26 (0.70 to 2.28)	1.07 (0.60 to 1.91)	0.29
0.87 (0.42 to 1.77)	1.06 (0.85 to 1.33)	1.01 (0.81 to 1.27)	0.79 (0.44 to 1.44)	**IC**	**0.85 (0.75 to 0.97)**	0.63
1.02 (0.51 to 2.06)	**1.25 (1.04 to 1.51)**	1.19 (0.99 to 1.43)	0.94 (0.52 to 1.67)	**1.18 (1.04 to 1.34)**	**C**	0.22
0.42	0.77	0.66	0.29	0.63	0.22	**P-Score**

C. Population with non-brain metastases

AC	0.94 (0.70 to 1.25)	0.89 (0.67 to 1.19)	1.09 (0.80 to 1.48)	0.88 (0.68 to 1.14)	**0.75 (0.60 to 0.93)**	0.72
1.07 (0.80 to 1.42)	**DC**	0.95 (0.73 to 1.24)	1.16 (0.87 to 1.55)	0.94 (0.75 to 1.18)	**0.80 (0.66 to 0.97)**	0.56
1.12 (0.84 to 1.49)	1.05 (0.81 to 1.37)	**DTC**	1.22 (0.92 to 1.62)	0.99 (0.79 to 1.24)	0.84 (0.70 to 1.01)	0.44
0.92 (0.68 to 1.25)	0.86 (0.65 to 1.15)	0.82 (0.62 to 1.09)	**PC**	0.81 (0.63 to 1.05)	**0.69 (0.56 to 0.86)**	0.88
1.13 (0.88 to 1.46)	1.06 (0.85 to 1.33)	1.01 (0.81 to 1.27)	1.23 (0.96 to 1.59)	**IC**	**0.85 (0.78 to 0.97)**	0.40
1.33 (1.07 to 1.66)	**1.25 (1.04 to 1.51)**	1.19 (0.99 to 1.43)	**1.45 (1.17 to 1.80)**	**1.18 (1.04 to 1.34)**	**C**	0.01
0.72	0.56	0.44	0.88	0.40	0.01	**P-Score**

FIGURE 2
Hazard ratios (gray and brown cell) and p-values (blue cell) of the network meta-analysis of the progression-free survival in the overall population **(A)**, population with brain metastases **(B)**, and population with non-brain metastases **(C)**. AC, atezolizumab plus chemotherapy; DC, durvaluma plus

(Continued)

FIGURE 2 (Continued)
chemotherapy; DTC, durvalumab with tremelimumab plus chemotherapy; PC, pembrolizumab plus chemotherapy; IC, ipilimumab plus chemotherapy; C, chemotherapy.

The baseline results of the CEA indicated that atezolizumab plus chemotherapy and durvalumab plus chemotherapy were the most effective strategies and provided the best treatment outcome in the NBMs and BMs populations, respectively. When it talks about cost-effectiveness according to relevant studies, immuno-chemotherapy regimens would be favored by clinical cases having reduced HRs for OS, while in patients with higher HRs it can become worse than chemotherapy (25, 31). Although atezolizumab plus chemotherapy and durvalumab plus chemotherapy provided 1.02 and 0.89 QALYs in patients with NBMs and BMs, respectively, whose QALYs were much higher than the other four treatment measures, they increased the survival benefit by 0.25 and 0.12 QALYs and the additional cost of $80,363 and $74,562, resulting in an ICER = 321,452 and 621,350/QALY, that is higher than WTP in the US, making it not cost-effective, in comparison to chemotherapy, respectively. Finally, modeling outcomes demonstrated that neither treatment plans were cost-effective in comparison to chemotherapy, in line with outcomes of several past investigations. However, chemotherapy alone was not enough to greatly improve the survival and prognosis of patients with ES-SCLC. Therefore, in addition to chemotherapy in first-line treatments, the most effective treatment strategy was to use atezolizumab plus chemotherapy for NBM cases and durvalumab plus chemotherapy for BM cases. Sensitivity analysis shows that the utility of PD was the most important factor influencing ICER value, followed by the incidence of AEs, and the price of ICIs are also factors that cannot be ignored. Since the price of ICIs is much higher than chemotherapy in the US, subsequent probabilistic sensitivity analysis results confirmed that atezolizumab plus chemotherapy and durvalumab plus chemotherapy were cost-effective in 32, 29, and 12%, 39% of the overall population and population with BMs, respectively. The results of the acceptable curve revealed that the US-based ICER value was affected by the shift in WTP value, while the US-based WTP value was affected by the *per capita* GDP. The average *per capita* US-based GDP value was adopted in our investigation (32). However, the *per capita* GDP of different regions in the US varies, so for several economically underdeveloped regions, the optimal strategy could be chemotherapy among the overall population. Regarding economically developed regions, atezolizumab plus chemotherapy and durvalumab plus chemotherapy were the preferred treatment options for the overall population and brain metastases, respectively.

The current assessment has several implications. On the one hand, patient survival has improved significantly with the introduction of ICIs. However, data was scarce for its efficacy within BM cases, and few clinical trials have been conducted for BMs alone. Patients with BMs were either excluded or only included in subgroups within key trials. The brain micro-environment itself has immunosuppressive effects, so it can promote the development of various tumor tissues and block anti-tumor immune responses (33–35). It is currently well established that chemotherapy can increase the efficacy of ICIs (36). Therefore, combination strategies may be more appropriate. For ES-SCLC, only the CASPIAN trial among our included studies demonstrated a trend of OS benefit in a small subgroup of patients with baseline BMs (55/805, 7%). HR for OS was 0.79 (95% CI, 0 44 to 1.41) (10). In non-small cell lung cancer (NSCLC), Powell et al. conducted a meta-analysis for three trials KEYNOTE-189,021, and

TABLE 2 Baseline results.

Treatment	Total cost $	LYs	ICER $/LY [a]	QALYs	ICER $/QALY[b]
Overall population					
Chemotherapy	133,625	1.44	NA	0.77	NA
Atezolizumab plus Chemotherapy	213,988	1.91	170,985	1.02	321,452
Durvaluma plus Chemotherapy	229,620	1.90	208,685	1.01	399,978
Pembrolizumab plus Chemotherapy	241,682	1.80	300,158	0.93	675,358
Ipilimumab plus Chemotherapy	568,657	1.55	3,954,836	0.85	5,437,894
Population with brain metastases					
Chemotherapy	133,625	1.44	NA	0.77	NA
Atezolizumab plus Chemotherapy	181,487	1.49	957,240	0.81	1,196,550
Durvaluma plus Chemotherapy	208,187	1.67	324,183	0.89	621,350
Pembrolizumab plus Chemotherapy	191,643	1.19	Dominated[c]	0.64	Dominated[c]
Ipilimumab plus Chemotherapy	517,993	1.15	Dominated[c]	0.65	Dominated[c]
Population with non-brain metastases					
Chemotherapy	133,625	1.44	NA	0.77	NA
Atezolizumab plus Chemotherapy	202,362	1.71	254,582	0.93	429,606
Durvaluma plus Chemotherapy	205,489	1.64	359,320	0.87	718,640
Pembrolizumab plus Chemotherapy	235,428	1.63	535,805	0.85	1,272,538
Ipilimumab plus Chemotherapy	540,073	1.45	40,644,800	0.79	20,322,400

[a]Compared to Chemotherapy ($/LY).
[b]Compared to Chemotherapy ($/QALY).
[c]Treatment showed lower effectiveness and higher cost, as compared with the chemotherapy.
ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.

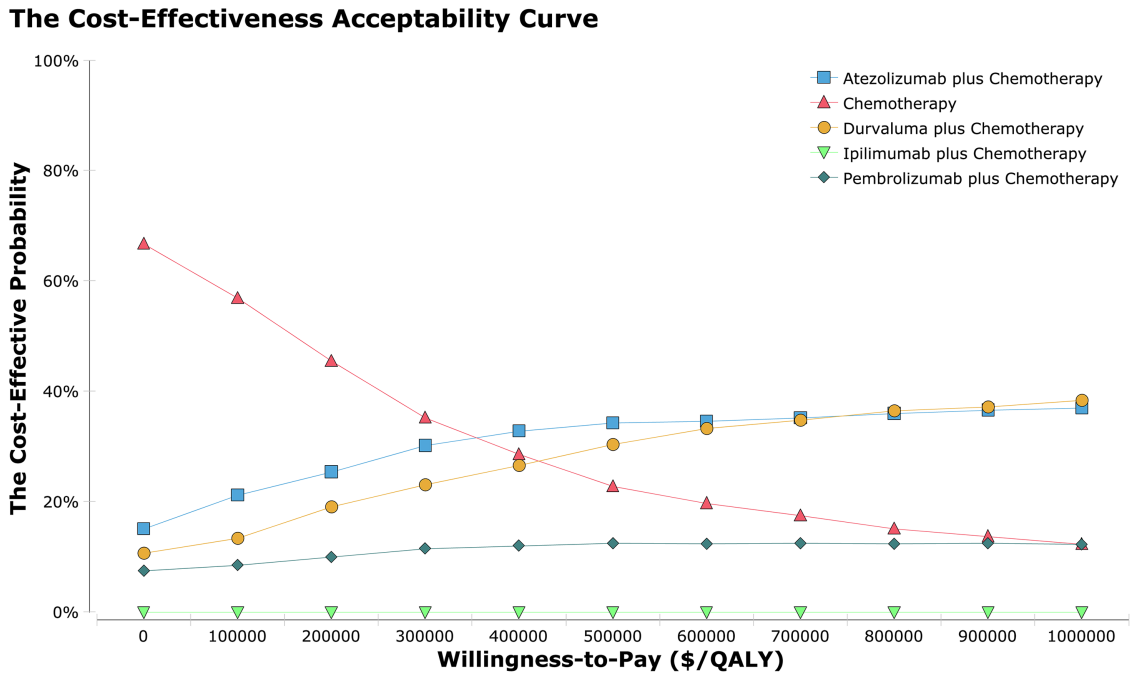

FIGURE 3
The cost-effectiveness acceptability curves for the atezolizumab plus chemotherapy, durvaluma plus chemotherapy, pembrolizumab plus chemotherapy, ipilimumab plus chemotherapy strategies compared to the chemotherapy strategy in the overall population.

407, including baseline BMs (171/1298, 13%), and concluded that HR for OS was 0.48 (95% CI, 0.32 to 0.70) in the baseline BMs group treated with immuno-chemotherapy. In melanoma, the NIBIT trial included asymptomatic BM patients (n = 20/86, 36%) with a median OS of 12.7 months (95% CI, 2.7 to 22.7) (37). It should be noted that, from the perspective of patients with BMs and ES-SCLC, the high price of anti-cancer drugs can make cancer patients face huge financial toxicity (38). Regarding the balance of the health care system, ensuring that patients with specific characteristics have access to safe, effective, and innovative treatments is as important as minimizing economic toxicity.

On the other hand, immunotherapy was improving the therapeutic efficacy of SCLC. Physicians and administrators need to select proper patients who can benefit from this type of therapy to maintain our healthcare system and establishing prognostic and response predictive markers was critical. PD-L1 expression, tumor mutational burden (TMB), and tumor-infiltrating lymphocytes (TILs) can be reliable prognostic biomarkers in small-cell lung cancer (SCLC) (39–41). However, our study did not perform an analysis of biomarkers, so further studies are needed in future work to explore biomarkers to determine which patients with heterogeneous diseases are likely to benefit more from treatment so that treatment can be tailored to the individual.

Although this study has important strengths, some limitations should be considered. Firstly, when using the NMA method to indirectly compare immuno-chemotherapy regimens, we assumed that the included studies did not differ in patient characteristics and summarized the chemotherapy groups. Secondly, the inference of long-term survival benefit is depending upon short-term survival data of each experiment, which will alter upon change of long-term follow-up. This is an inevitable limitation in our model. Consequently, it is necessary to evaluate the concordance of such modeled health outcomes with real-world data. Thirdly, for enhanced analysis, this investigation assumed that all chemotherapy regimens used carboplatin, which was safer in the clinic. The cost of carboplatin was higher than that of cisplatin, so the cost of chemotherapy can be overestimated. However, sensitivity analysis demonstrated that the cost of carboplatin has little impact on the model results. Fourthly, several trials lacked survival data from subgroups, and the original group balance was produced by Hoyle's methods. Consequently, the results of the subgroups analysis should be interpreted carefully. Fifth, this investigation analyzed the cost-effectiveness of patients with or without BMs. However we did not investigate the economic results of other subgroups, such as age, gender, smoking status, and liver metastasis. Sixth, due to the lack of complete QoL data to calculate the utility values, we referred the mean health utility value of NSCLC in PD state, and corrected the utility values by considering the disutility values of AEs and only 3/4 AEs were included, which might lead to overestimates or underestimates of the utility values. Finally, this investigation did not include social costs, including those related to the informal and non-health sectors.

In conclusion, immuno-chemotherapy regimens appear to be superior to standard chemotherapy. Among the five immuno-chemotherapy strategies, atezolizumab plus chemotherapy regimen seem to have the best effect on ES-SCLC patients other than BMs; durvalumab plus chemotherapy option can be a favorable condition for the population with BMs. Whereby, from the perspective of the US payer, the first-line use of four clinically effective immuno-chemotherapy regimens to treat ES-SCLC patients is not cost-effective in comparison to chemotherapy, though atezolizumab plus

chemotherapy regimen can provide a more effective balance across ICER and QALYs in the overall population. Within BM clinical cases, durvalumab plus chemotherapy program obtain more health benefits. This finding can help physicians make decisions in clinical work and aid policy formulation in medical reimbursement.

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.

Ethics statement

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, it does not require the approval of the independent ethics committee.

Author contributions

YZ, KL, QY, MZ, and LP: designed experiment, analyzed the data, wrote the manuscript, and complete the revision. YZ and KL: performed the experiments. LP and MZ: contributed analysis tools and funding. All authors have read and approved the manuscript.

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All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1028202/full#supplementary-material

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From hazard identification to risk assessment: The role of the prevention technician in the carcinogenic risk assessment for formaldehyde

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The Prevention Technician in the Environment and Workplaces (PTEW) is a health professional who works in the identification, assessment, and management of risk in living and working places. The PTEW implements specific corrective actions at reducing exposure levels to chemicals such as formaldehyde. The aim of this report was to update the formaldehyde risk assessment document (RAD). The risk assessment process was divided into three steps as follows: (1) preliminary data collection, (2) an on-site visit to identify the use patterns and process, and (3) application of the algorithm to calculate the exposure levels of healthcare workers. In addition, with the introduction of closed-circuit systems, 23 devices were evaluated to identify possible airborne dispersion of formaldehyde. The algorithm was applied in 31 hospital units and the results allowed us to classify the staff in two levels of exposure for each hospital unit; healthcare workers were classified as "exposed" or "potentially exposed." Most of the HCWs are categorized as potentially exposed, and only workers working in laboratories are considered to be exposed. The results showed that devices must be used properly according to the user manual. To increase the level of worker safety, we have proposed to introduce closed-circuit safe handling systems and keeping the duration and intensity of exposure at the lowest possible levels according to the "ALARA" principle. The assignment of the Italian PTEW is to achieve excellence in the levels of health and safety of patients and hospital workers by pursuing a shared mission: improving the quality of public health.

KEYWORDS

Cancerogen, formaldehide, risk assesment, hazard identification, algorithm

Introduction

The Prevention Technician in the Environment and Workplaces (PTEW) is a health professional who deals with the identification and characterization of risk in living and working places. One of the main tasks is to evaluate exposure to various substances, including carcinogens. The PTEW participates in different stages of risk management

activities: inspections, hazard identification, risk assessment, environmental monitoring, and improvement proposals (1).

The risk assessment is the first among the general measures for the protection of the health and safety of workers. It is the tool used to guide and define preventive interventions (elimination, reduction, and/or control of risks), to plan information and training activities on risks and the protective measures adopted, and to observe the health status of workers (2). In addition, risk assessment is based on the acquisition of general theoretical scientific knowledge and carrying out field investigations (environmental and biological monitoring), leading to the estimation of the degree of exposure. Activities related to risk assessment include different aspects involving different professionals with distinct levels of responsibility (3).

The PTEW works in a team with different health professionals in departments of the territory that are essential for the identification of critical issues. Moreover, the PTEW identifies specific improvement measures aimed to reduce the concentrations of the dangerous substance (4, 5).

One of the agents for which an occupational exposure risk assessment is required is formaldehyde, which as of 2014 meets the criteria for classification as a carcinogen in Group 1B, according to EU Regulation N. 605/2014 (6). Internationally, as early as 15 July 2004, the International Agency for Research on Cancer (IARC) confirmed the carcinogenic effect of formaldehyde (7–10), before being classified only as a dangerous substance.

In Italy, for work activities involving exposure to formaldehyde, reference is made to Legislative Decree No. 81/2008—transposition of EU Directive 89/391/EEC (81/08) "protection from carcinogens and mutagens," which defines the preventive actions to be implemented in workplaces in case of the use of carcinogens and/or mutagens.

The first recommendation is not to use and reduce the use of the substance and to replace it, if technically possible, with a chemical substance or mixture or process that is not harmful to health and safety.

If it is not technically possible, the carcinogens and/or mutagens must be replaced, ensuring that the production and/or use takes place in a closed system, and finally, if the previous measures are not feasible, the level of workers' occupational exposure must be reduced to the lowest value (11, 12).

In Italy, a chemical frequently used in healthcare settings that requires a mandatory process of risk assessment is formaldehyde.

The use of formaldehyde in hospital settings is indispensable. However, technological advances offered by the healthcare technology and medical device market can enable the safe use of formaldehyde.

Although there are many studies highlighting how air ventilation, the use of "formaldehyde-free" chemicals, and continuous monitoring reduce occupational formaldehyde exposure, in recent years, closed-loop systems have been marketed of which a few studies assess formaldehyde dispersion (13–15).

The aim of this brief report is to analyze the methodological approach of workers' carcinogenic risk management for the use of formaldehyde in healthcare work processes and closed-loop system dispersion assessment.

Methods

The opportunity for this brief research report comes from the need to update the formaldehyde risk assessment document (RAD) in a University Hospital. The RAD is mandatory in Italy, according to Legislative Decree No. 81/2008.

Formaldehyde risk assessment document

The first step of the risk assessment was data collection, i.e., a census was conducted to verify the hospital units where formaldehyde is used, and the annual quantity is used.

The second step was an on-site visit to identify formaldehyde as it was used and work processes. During this phase in hospital units, a checklist was applied. The information collected with the checklist was as follows:

- User's professional role (physician, nurse, and technician).
- The number of people using the substance.
- Quantity of formaldehyde used in each process.
- Exposure time.

This information is essential to implement formaldehyde risk assessment and is used to estimate healthcare workers' (HCWs) exposure through an algorithm, in compliance with the National Agencies for Environmental Protection ISPRA and ENEA (16).

In the third step, the algorithm was applied to calculate the exposure levels of healthcare workers (HCWs), according to the following formula:

$$\text{Hcanc}\left(\text{cancerogenic hazard}\right) = \text{P} \times \text{CH} \times \text{T} \times \text{Q} \times \text{M} \times \text{F}$$

where

- P: use and efficiency of PPE.
- CH: chemical/physical (gas, vapor, volatile liquid, and solid).
- T: temperature of the working process.
- Q: quantities used for each process.
- M: handling time (min/day).
- F: use frequency (days/year).

Table 1 shows that for each risk factor, a hazard score was attributed, depending on the risk category.

Environmental sampling of closed-circuit security devices

During the period between November 2017 and October 2022, 23 closed-circuit systems were tested to assess the seal of the device to prevent any airborne leakage of formaldehyde. Table 2 shows the characteristics of the devices.

For airborne formaldehyde, measurements were used as a portable gas detector (RIKEN KEIKI HCHO Detector Mod. FP40). The measurement range is from 0.01 to 0.4 parts per million (ppm), with an interval of 0.01 ppm, and the value is

TABLE 1 Hazard score for each risk category.

Risk factor	Risk category		Hazard score
P	Closed loop and chemical hood		2
	Partially under chemical hood		5
	No chemical hood		10
CH	Gel,solid, compactn		2
	Non-volatile liquid, crystals		5
	Gas, volatile liquid vapor, fine dust		10
Q	<1 g	<1 ml	2
	1–50 g	1–50 ml	5
	>50 g	>50 ml	10
M	Minutes/Days		Minutes/480 (Working Minutes/Day)
F	Minutes/Years		Minutes/230 (Working Days/Year)

TABLE 2 Characteristics of the devices.

Id	Oevice capacity	Formaldeh yde	Buffer	Buffered formaldehyde	Batch	Expiration date
01		10 ml			00013	12/2018
02		20 ml			00004	06/2020
03		60 ml			00006	06/2020
04		900 ml			000020	01/2021
05		30 ml			1702	01/2022
06		60 ml			1729	07/2022
07		30 ml			201704	04/2019
08		90 ml			11601707	02/2019
09		10 ml			4117	10/2019
010		60 ml			00006	06/2020
011		20 ml			201711	11/2019
012		20 ml			201711	11/2019
013	60 ml	10 ml	10 ml		1806/6	06/2020
014	150 ml	60 ml		60 ml	1806/3	06/2020
015	60 ml	20 ml		20 ml	175/3	05/2019
016		110 ml	110 ml		1805/2	05/2022
017	40 ml			20 ml	00142	05/2022
018	60 ml	7 ml		33 ml	2022 × 00012	01/2024
019	60 ml	7 ml		33 ml	2022 × 00012	01/2024
020	250 ml	19 ml		110 ml	2022 × 31632	11/2022
021	90 ml				1130	03/2026
022	90 ml				1130	03/2026
023	90 ml				1130	03/2026

expressed as <0.01 ppm, which was the detection limit of the instrument.

The standard measurement time was 3 min, after which the measurement results are readable on the instrument display.

The laboratory tests were carried out with the use of collective protective equipment (work under a chemical fume hood) and personal protective equipment (nitrile gloves as per the material safety data sheet indications of formaldehyde) to reduce any personnel exposure to a residual level.

The following measurement protocols were performed:

T1: device not used.

T2: immediately after device use.

T3: after 10 min after device use.

T4: after 1 h after device use.

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T5: after 24 h after device use.

Before sampling, preparation of the instrumentation was carried out as follows:

- Cleaning the instrument measurement system, i.e., flushing the cell and internal duct by aspiration in air potentially formaldehyde free (outside air) for ~10 min.
- Cleaning of the system was repeated when the instrument measured the upper limit of the range (>0.4 ppm).
- In all other cases, several cycles of "refresh," i.e., vacuum cleaning of the system, were performed between measurements.
- Measurements were made inside a glass container with a volume of ~10 L equipped with an air inlet valve.

Results

The algorithm was applied in 31 hospital units, and the results allowed us to classify the staff into two levels of exposure for each hospital unit; the HCWs were classified as "exposed" or "potentially exposed."

Table 3 shows the results of the evaluation by individual healthcare professional category.

Most of the healthcare categories result as potentially exposed, the hospital units with the doctor category potentially exposed were 25 (80.6%), and the hospital units with the nurse category potentially exposed were 21 (67.7%); however, the hospital units with the technician category potentially exposed were 3 (9.7%).

Table 4 shows the results of the environmental samplings to assess the seal of the device.

TABLE 3 Results HCWs potentially exposed or exposed in hospital unit.

Hospital units *N* =31	HCWs potentially exposed in HU *n* (%)	HCWs exposed in HU *n* (%)
Doctor	25 (80.6)	2 (6.4)
Nurse	21 (67.7)	2 (6.4)
Midwife	3 (14.2)	0 (0.0)
Technician	1 (4.8)	3 (9.7)

HU: hospital unit.

TABLE 4 Environmentlsamplings of the closed-circuit devices.

ID	T1 (ppm) (PPM)	T2 (ppm)	T3 (ppm)	T4 (ppm)	T5 (ppm)
1	<0.01	<0.01	<0.01	0.02	0.04
2	<0.01	<0.01	<0.01	0.03	0.09
3	0.01	0.01	<0.01	<0.01	0.14
4	0.01	0.01	<0.01	<0.01	0.07
5	0.01	0.07	0.1	0.26	**>0.4**
6	<0.01	0.05	0.07	0.21	**>0.4**
7	<0.01	<0.01	<0.01	<0.01	0.01
8	<0.01	0.01	0.01	0.06	**>0.4**
9	<0.01	0.09	**>0.4**	**>0.4**	**>0.4**
10	0.07	0.02	0.06	0.1	0.28
11	<0.01	0.22	**>0.4**	**>0.4**	**>0.4**
12	<0.01	0.31	**>0.4**	**>0.4**	**>0.4**
13	0.05	0.06	0.07	0.13	0.25
14	0.12	0.12	0.12	0.12	**>0.4**
15	<0.01	0.03	0.1	0.15	**>0.4**
16	<0.01	<0.01	<0.01	0.06	0.06
17	**>0.4**	**>0.4**	**>0.4**	**>0.4**	**>0.4**
18	0.01	**>0.4**	**>0.4**	**>0.4**	**>0.4**
19	<0.01	0.05	0.06	0.06	0.04
20	0.01	<0.01	<0.01	0.25	0.18
21	0.02	<0.01	0.01	<0.01	<0.01
22	0.01	<0.01	0.01	<0.01	0.02
23	0.02	0.01	0.01	<0.01	0.03

Bold value indicates are measured values but out of the measurement scale.

Discussion

In relation to the results, corrective actions were implemented, to ensure workers' health and safety levels over time:

1. **Closed-circuit safety device** was introduced for the safe handling of small histological biopsy.
2. **Purchase of closed-circuit safety equipment** for handling jugs with formaldehyde. In hospital units, where is not possible to use the closed-circuit safety jug because of the handling of large anatomical pieces, the risk of exposure for healthcare professionals remains higher.
3. **Environmental sampling**: In total, 23 different types of closed-circuit safety were tested to verify the seal of the device. Furthermore, three closed-circuit safety equipment for the automatic filling of large containers were evaluated to verify the level of dispersion of formaldehyde vapors during their use. The data show that if the device is used correctly, the levels of environmental contamination are to be considered harmless; on the contrary, if the device is not used correctly, the contamination levels exceed the measurement range.
4. **Accidental spill containment kit**: A kit has been prepared for use in the event of an accidental formaldehyde spill. The kit consists of the necessary personal protective equipment (PPE), neutralizing cloths, a bag, and a bucket for disposal. In addition, training was conducted on the proper use of the emergency kit. These kits have been stocked in all hospital units where it is necessary to store formaldehyde containers.
5. **Updating of the accidental spill procedure**: The internal procedure was updated with a description of the new operating instructions to be adopted in the case of accidental spillage of small quantities (≥10 ml to ≤10 L) of hazardous substances or chemicals. The new internal procedure was implemented to reduce the risk and define the area to be isolated and cleaned, according to the new material safety data sheet.
6. **Training**: The training was planned for work classified as "exposed" and organized into three courses each lasting 2 h.

The total number of workers who participated was 75. Topics were an update on the appropriate use of formaldehyde in accordance with the internal procedure, the proper use of new closed-circuit safety devices, PPE to be used, and what to do in case of an accidental spill.

Conclusion

The results showed that devices must be used properly, according to the user manual, to avoid any contamination.

The application of a risk assessment methodology is critical to evaluate healthcare professionals' exposure to formaldehyde. This methodology estimates the efficacy of a series of protective actions for the health and safety of workers and how to better manage the risk.

To increase the level of worker safety, we have proposed to introduce closed-loop or safe handling systems and keeping the duration and intensity of exposure at the lowest possible levels, according to the "as low as reasonably achievable" (ALARA) principle (17).

The formaldehyde risk assessment and management are considered a priority for the health and safety of HCWs and involve a multidisciplinary group to develop a method of updating the risk assessment considering international and national laws and guidelines.

The task of the Italian Prevention Technician is to achieve excellence in the levels of health and safety of patients and hospital workers by pursuing a shared mission: improving the quality of public health.

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

FP, FT, MW, FB, RG, and RS had the idea and contributed to the writing of the text. PL carried out the final revision. All authors contributed to the article and approved the submitted version.

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.

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Cost-effectiveness analysis of trastuzumab deruxtecan in patients with HER2-low advanced breast cancer based on DESTINY-Breast04

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Background and purpose: Breast cancer is a rapidly raising healthcare problem worldwide. DESTINY-Breast04 demonstrated that trastuzumab deruxtecan (T-Dxd) had a survival advantage comparing to the physician's choice of chemotherapy for patients with HER2-low metastatic breast cancer. But at the same time, this expensive novel treatment also brought an economic burden. This study assessed the cost-effectiveness of T-Dxd based on results of DESTINY-Breast04 from the perspective of Chinese healthcare system.

Materials and methods: A three-state partitioned-survival model [progression-free survival (PFS), progressive disease (PD) and death] based on data from DESTINY-Breast04 and Chinese healthcare system was used to estimate the incremental cost-effectiveness ratio (ICER) of T-Dxd vs. the physician's choice of chemotherapy for HER2-low metastatic breast cancer. Costs, quality-adjusted life-years (QALYs) and the ICER in terms of 2022 US$ per QALY gained were calculated for both hormone receptor–positive cohort and all patients. One-way and probabilistic sensitivity analyses were performed to assess the model robustness.

Results: Compared with the physician's choice of chemotherapy, T-Dxd increased costs by $104,168.30, while gaining 0.31 QALYs, resulting in an ICER of $336,026.77 per QALY in all patients. The costs of T-Dxd and the utility of PFS were the crucial factors in determining the ICER. In the hormone receptor–positive cohort, the ICER was lower than that in all patients, with the ICER of $274,905.72 per QALY. The ICER was much higher than the commonly accepted willingness-to-pay threshold ($357,96.83 per QALY).

Conclusion: T-Dxd as second- or subsequent-line treatment is not a cost-effective treatment option for HER2-low metastatic breast cancer from the perspective of the Chinese healthcare system.

KEYWORDS

cost-effectiveness, breast cancer, HER2-low, trastuzumab deruxtecan, chemotherapy

1. Introduction

The burden of breast cancer is increasing rapidly. In 2020, there was an estimated 2.26 million new cases of breast cancer, making it the most commonly diagnosed cancer globally, surpassing even lung cancer. Breast cancer also created 684,996 deaths worldwide, ranking fifth among all cancer-related deaths (1). The age-standardized incidence and mortality rate of breast cancer have significantly increased in China during the past decade, putting a great burden on Chinese healthcare and economic system (2). Human epidermal growth factor receptor 2 (HER2)-low breast cancer, defined as HER2 immunohistochemistry (IHC) 1+ or IHC 2+ and insituhybridization (ISH)-negative, accounts for 40–50% of all breast cancers (3, 4). Previous HER2-targeted therapies remarkably improved clinical outcomes of HER2 positive breast cancer, but have failed to provide prognosis benefit in patients with HER2-low breast cancer. There is limited treatment option for progressed HER2-low breast cancer refractory to standard treatment, and patients often have to receive palliative chemotherapy. Therefore, creating effective new treatments for HER2-low breast cancer is of great clinical significance (5).

Trastuzumab deruxtecan (T-Dxd) is an antibody–drug conjugate (ADC) composed of trastuzumab and a topoisomerase I inhibitor through a tetrapeptide-based cleavable linker (6). Unlike many other HER2-targeted therapies, T-Dxd is also effective in HER2-low breast cancer due to its bystander effect (7, 8). The superiority of T-Dxd over traditional single-agent chemotherapy in patients with HER2-low breast cancer who had received one or two previous lines of treatment was demonstrated in DESTINY-Breast04 (9). Based on DESTINY-Breast04, the US Food and Drug Administration approved T-Dxd for patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting. The National Comprehensive Cancer Network (NCCN) also recommended T-Dxd as the preferred second-line therapy for HER2-low breast cancer (10).

However, while T-Dxd demonstrated survival advantage in DESTINY-Breast04, it is extremely expensive for both patients and insurance payers. As such, we sought to evaluate the cost-effectiveness of T-Dxd for advanced HER2-low breast cancer from the Chinese healthcare system perspective.

2. Methods

2.1. Patients and treatment

In the base case analysis, a hypothetical cohort was generated using the clinical information collected from DESTINY-Breast04 (9). The trial included a total of 557 HER2-low metastatic breast cancer patients, of whom 373 were randomly assigned to receive T-Dxd 5.4 mg/kg every 3 weeks (T-Dxd group) while 184 were assigned to the physician's choice of chemotherapy (chemotherapy group) when their breast cancer progressed after one or two previous lines of chemotherapy. 331 (88.7%) T-Dxd group patients and 163 (88.6%) chemotherapy group patients, respectively, were qualified for the hormone receptor–positive cohort. Treatment for chemotherapy group comprised of five regimens: capecitabine (20.1%), eribulin (51.1%), gemcitabine (10.3%), paclitaxel (8.2%), or nab-paclitaxel (10.3%). Overall survival (OS) and progression-free survival (PFS) were evaluated in the hormone receptor–positive cohort and in all patients.

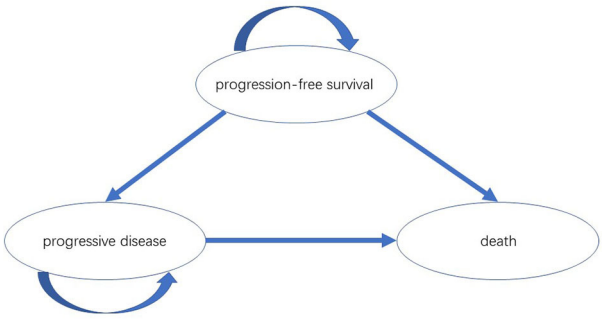

FIGURE 1
The partitioned-survival model simulated three health states: PFS, PD and death. PFS, progression-free survival; PD, progressive disease.

2.2. Model structure and assumptions

A partitioned-survival model was constructed by Treeage Pro Suite 2019 (Treeage Software, Inc., MA, USA) from the perspective of the Chinese healthcare system. The model included three mutually exclusive health states: PFS, progressive disease (PD) and death. The initial state was assumed to be PFS, and patients could remain in the PFS state or move to PD or death state during each cycle (Figure 1). We assumed that the cycle length was 1-month based on the time span of disease duration and progression. Patients with metastatic HER2-low breast cancer refractory to standard therapies have poor prognosis; the median overall survival ranged from 11.1 to 29.4 months (8, 9, 11). The population in the PSM model had received one or two previous lines of chemotherapy, and the median overall survival in DESTINY-Breast04 was less than two years (9). Therefore, a 5-year time horizon was selected for the model. The annual discount rates for costs and outcomes were set at 5% as recommended by guidelines, and discount rates of 0 and 8% were explored in scenario analyses (12). The threshold of willingness to pay (WTP) was assumed to be three times the Chinese per Gross Domestic Product per capita (GDP) according to WHO guideline (13). As a result, $357,96.83/quality-adjusted life-year (QALY) was set according to per capita GDP of China 2021 released by National Bureau of Statistics. All costs were converted into US dollars, with an exchange rate of $1 = ¥6.7863 (17 Aug 2022).

2.3. Clinical parameters from DESTINY-Breast04

Clinical data on efficacy and safety were obtained from DESTINY-Breast04. Survival parameters were obtained by

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digitizing the Kaplan– Meier (KM) curve (OS, PFS) of DESTINY-Breast04. Individual patient data were reconstructed using the method described by Guyot et al. (14). KM curves up to the end of follow-up period were followed by simulative curves generated from best-fit parametric distributions. Different parameter distributions (Exponential, Gamma, Gen gamma, Gompertz, Weibull, Log-logistic, Log-normal) were applied to fit the reconstructed OS and PFS curves. The best-fit parametric distributions were selected based on Akaike information criterion (AIC), Bayesian information criterion (BIC) and visual inspection. The IC values for all models were shown in Table 1.

In the hormone receptor–positive cohort, Weibull distribution was selected to fit the KM curves for OS of both T-Dxd and chemotherapy group; for PFS, Gen gamma and Log-normal distribution were chosen for T-Dxd and chemotherapy group, respectively. Among all patients, Weibull distribution and Log-logistic distribution were found to fit the OS curve of the T-Dxd and the chemotherapy group, respectively; Gamma distributions and Log-normal distributions were selected to fit the PFS curve of the T-Dxd and the chemotherapy group, respectively. The original and the fitting curves were shown in Figure 2.

The incidence of adverse events (AEs) required to estimate the management cost of AEs was obtained from DESTINY-Breast04, more details ware shown Table 2. As quality-of-life data was not collected in DESTINY-Breast04, health state utility scores were derived from previously published literature. The utility values of PFS state, PD state and death were 0.843, 0.60 and 0, respectively (15).

2.4. Cost estimates

Direct medical costs consisted of drug treatment costs, AEs treatment costs, follow-up costs, hospital service costs, and best supportive care (BSC) costs, were estimated from the perspective of the Chinese healthcare system. Resource costs except for the drug treatment costs were obtained from Chinese studies.

Destiny-break04 did not provide a subsequent treatment plan for patients whose diseases progressed on T-Dxd or physician's choice of chemotherapy; according to the guideline, BSC is recommended for these patients as they have already received two lines of therapy (16). Costs related to subsequent BSC were derived from published literatures (17). The dosages of chemotherapy agents and T-Dxd were calculated based on standard human body surface area of 1.72 m^2 and a standard female bodyweight of 55 kg, respectively (18). Although T-Dxd is yet to be approved for Chinese market, it became available in Hainan's Boao Lecheng International Medical Tourism Pilot Zone in February 2022. For this study, the price for T-Dxd in Chinese market was set with reference to the marketing price of T-Dxd in Boao. Prices of other drugs used in this study were calculated based on the median winning prices of the bid-winning products on https://www.yaozh.com/.

DESTINY-Breast04 reported data on incidences of adverse events (AEs). Only the costs related to managing grade 3 or higher AEs were included for this study; grade 1–2 AEs were considered manageable within standard patient monitoring. The costs of managing grade 3–5

TABLE 1 Results of the fit to the observed data.

	Hormone receptor–positive cohort								All patients							
	OS of T-DXd		PFS of T-DXd		OS of chemotherapy		PFS of chemotherapy		OS of T-DXd		PFS of T-DXd		OS of chemotherapy		PFS of chemotherapy	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	1,149.75	1,153.55	1,493.30	1,497.10	647.67	650.76	618.79	621.88	1,313.07	1,316.99	1,755.62	1,759.54	730.71	733.93	725.48	728.69
Gamma	1,124.76	1,132.36	1,479.33	1,486.94	636.17	642.36	613.11	619.30	1,276.44	1,284.28	1,742.46	1,750.30	709.42	715.85	717.89	724.32
Gen gamma	1,122.53	1,133.93	1,477.94	1,489.35	637.56	646.85	601.61	610.89	1,278.18	1,289.94	1,742.19	1,753.95	711.28	720.92	703.71	713.36
Gompertz	1,121.52	1,129.12	1,489.99	1,497.60	638.57	644.75	620.56	626.74	1,284.91	1,292.76	1,751.28	1,759.12	719.06	725.49	727.20	733.63
Weibull	1,121.87	1,129.48	1,481.73	1,489.33	635.57	641.76	615.93	622.12	1,276.28	1,284.13	1,744.41	1,752.25	710.68	717.11	721.55	727.98
Log-logistic	1,125.70	1,133.31	1,478.45	1,486.05	636.57	642.75	606.70	612.88	1,276.86	1,284.70	1,745.00	1,752.84	708.48	714.91	709.49	715.92
Log-normal	1,143.33	1,150.94	1,478.04	1,485.64	645.34	651.53	601.35	607.54	1,284.34	1,292.18	1,744.78	1,752.63	712.74	719.17	703.39	709.82

AIC, Akaike information criterion; BIC, Bayesian Information Criterion; OS, Overall Survival; PFS, Progression-Free Survival; T-DXd, Trastuzumab Deruxtecan.

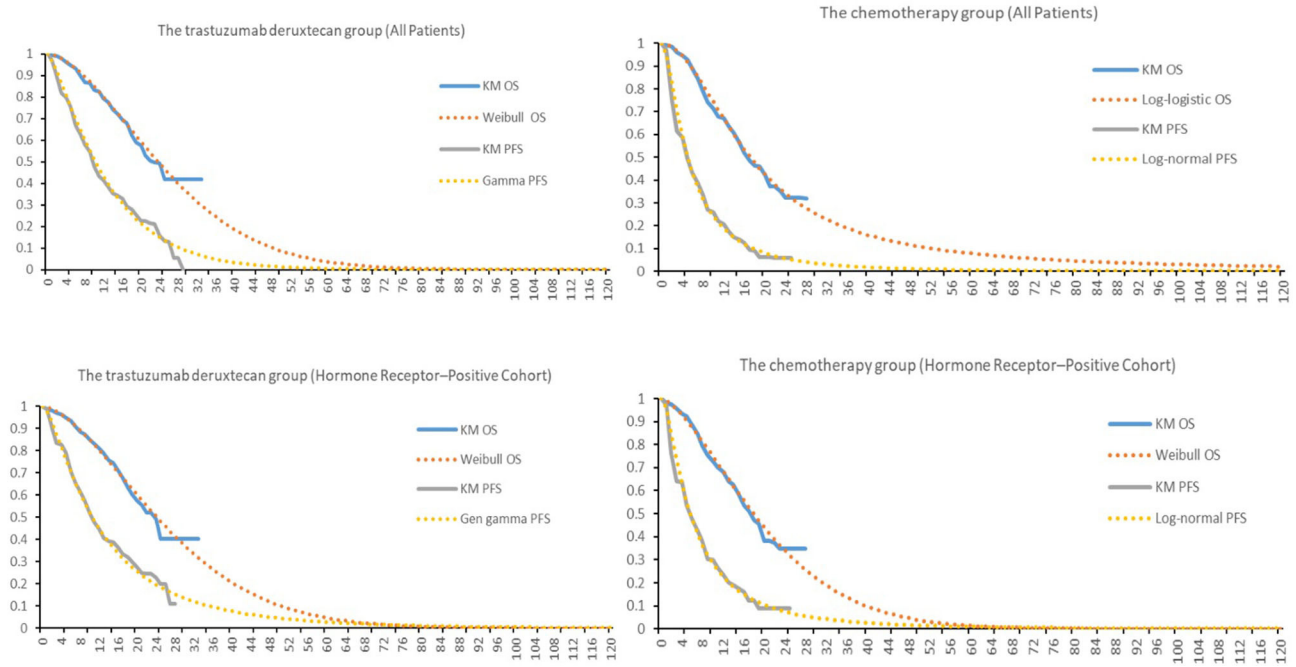

FIGURE 2
Kaplan-Meier survival for the trastuzumab deruxtecan and chemotherapy groups in DESTINY-Breast04 and the fitting curves. OS, overall survival; PFS, progression-free survival.

TABLE 2 Clinical information based on DESTINY-Breast04.

Variables	T-DXd	Chemotherapy
OS (months)		
All patients	23.4	16.8
Hormone receptor–positive cohort	23.9	17.5
PFS (months)		
All patients	9.9	5.1
Hormone receptor–positive cohort	10.1	5.4
Probability of grade 3/4 AEs		
Neutropenia	13.70%	40.70%
Anemia	8.10%	4.70%
Thrombocytopenia	5.10%	0.60%
Leukopenia	6.50%	19.20%
Nausea	4.60%	0.00%
Vomiting	1.30%	0.00%
Diarrhea	1.10%	1.70%
Increased aminotransferase levels	3.20%	8.10%
Fatigue	7.50%	4.70%
Decreased appetite	2.40%	1.20%

OS, Overall Survival; PFS, Progression-Free Survival; T-DXd, Trastuzumab Deruxtecan.

AEs were derived from previously published economic studies (18–23). Detailed information was shown in Table 3.

2.5. Sensitivity analysis

One-way sensitivity analysis and probabilistic sensitivity analyses (PSA) were performed to examine the potential influence on the results. In one-way sensitivity analysis, the most parameters of costs and utilities were varied at a range of ± 20% of their baseline value, and the range of discount rate was from 0 to 8%. Since T-Dxd has not been approved in Chinese Mainland, the price of trastuzumab deruxtecan may decrease sharply in the future. Therefore, the minimum cost of T-Dxd was set to a 50% decrement from the baseline value. The One-way sensitivity analysis results were presented in a tornado diagram. A PSA was performed by using Monte Carlo simulation of 1,000 iterations to assess the robustness of the estimated cost-effectiveness ratio. Gamma and Beta distributions were adopted for costs and utilities, respectively. The results of the PSA were represented by an acceptable curve and incremental cost-effectiveness scatter plot.

3. Results

3.1. Base-case analysis

In the base-case analysis, among all patients, the total cost was $145,887.58 for the T-Dxd group and $41,719.28 for the chemotherapy group. The overall QALYs in the T-Dxd group were higher than that in the chemotherapy group (1.57 QALYs vs. 1.26 QALYs). The incremental cost-effectiveness ratio (ICER) was $336,026.77 per QALY, which was more than 9 times the WTP threshold for cost-effectiveness ($357,96.83 per QALY in China). In the hormone receptor–positive cohort, the T-Dxd group comprised

TABLE 3 Base-case model inputs.

Parameter	Value
Cost	
T-DXd per 100 mg	2,431.37
Capecitabine per 0.5 g tablet	12.11
Paclitaxel	37.79
Nab-paclitaxel (per 100 mg)	114.94
Hospitalization per cycle	57.43
Post-progression per cycle	1,886.67
Follow-up per cycle	48.00
SAE management cost per event	
Neutropenia	547.50
Anemia	607.06
Thrombocytopenia	193.50
Leukopenia	104.95
Nausea	39.60
Vomiting	39.60
Diarrhea	44.30
Increased aminotransferase levels	68.30
Fatigue	131.78
Decreased appetite	115.40
Utilities	
PFS	0.843
PD	0.6
Discount rate	5%

PD, progressive disease; PFS, Progression-Free Survival; SAE, Serious Adverse Event; T-DXd: Trastuzumab Deruxtecan.

even higher QALY. The T-Dxd group cost $118,209.46 more than the chemotherapy group while providing additional 0.43 QALYs, leading to an ICER of $274,905.72 per QALY in the hormone receptor–positive cohort. The details are listed in Table 4.

3.2. Sensitivity analysis

The results of the one-way sensitivity analysis were shown in Figure 3. In both the hormone receptor–positive cohort and all patients, the cost of T-Dxd and the utility of PFS were the most influential factors on the results. In addition, the cost of chemotherapy and the utility of PD had moderate impact on ICER. Other parameters such as discount rate, costs of PD, AEs, hospitalization and follow-up had minor impact on the robustness of the cost-effectiveness analysis. More details were shown in Figure 3.

T-Dxd would not be cost-effective unless the threshold of the CEA sharply raise to about $170,000–$225,000 per QALY (Figure 4), which seems impossible as China's GDP cannot reach this level in the short term. The PSA suggested that compared with chemotherapy, the probability of T-Dxd being cost-effective was 0% at the WTP threshold of $35,796.83/QALY in both all patients and the hormone receptor–positive cohort (Figure 5). The results of PSA demonstrated that the T-Dxd had no economic advantage over the traditional chemotherapy in China in the near future.

4. Discussion

DESTINY serial studies were launched since the approval of T-Dxd. DESTINY-Breast−02, 03 and 04 studies discovered positive results in T-Dxd groups, changing treatment paradigms in breast cancer (9, 24, 25). As a novel therapy, T-Dxd was associated with high economic burden; therefore, pharmacoeconomic research based on DESTINY trials was warranted to evaluate its cost-effectiveness (26–29). Previously, Zhu et al. conducted a Markov decision-analytic model to evaluate the cost-effectiveness of T-DXd for HER2-low metastatic breast cancer in the United States; their study demonstrated that T-DXd was not cost-effective for patients with HER2-low advanced breast cancer comparing to chemotherapy in the United States. However, by December 2022, there has been no pharmacoeconomic evaluation based on DESTINY-Breast04 from the perspective of Chinese healthcare system. In this study, we proved that T-Dxd was not cost-effective for advanced HER2-low breast cancer compared with chemotherapy from the perspective of Chinese healthcare system using a three-state partitioned-survival model. The price of T-Dxd had highest impact on the ICER, which also aligns with the result from Zhu et al.

In 2013, The State Council officially approved the establishment of Hainan Boao Lecheng International Medical Tourism Pilot Zone, making Boao Lecheng the only area in mainland China that can market drugs that have been approved abroad but not yet marketed in mainland China. The price of T-Dxd was set at the marketing price in Boao for this study, but it may substantially decrease in the next few years as with anticipation of national approval by 2023. At present, anti-tumor drugs must go through national medical insurance negotiations to enter the Chinese medical insurance formulary. In 2022, the average price reduction of 67 drugs upon entering the national medical insurance formulary was 61.71%. In the previous 3 years, the price reductions were 56.7, 60.7, and 53.8% respectively through negotiations led by the National Healthcare Security Administration. Considering the price of T-Dxd may drastically decreased when it enters the Chinese medical insurance formulary, the minimum cost of T-Dxd was set to a 50% decrement from the baseline value in the one-way sensitivity analysis. However, even with the 50% price decrease, the resulting ICER of $162,768.63 per QALY was still much higher than the preset WTP.

WTP is a critical parameter to determine whether the treatment is cost-effective. When the ICER was lower than the WTP, the treatment was considered to be favorably cost-effective. Currently, the WHO standard of WTP setting at 1–3 times GDP per capita is still widely used (30, 31). However, some studies have suggested that three times of GDP per capita is too high for WTP (32, 33). For patients at end of life, the National Institute of Health and Clinical Excellence (NICE) have raised the WTP threshold for life-extending treatments that are not considered cost-effective

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TABLE 4 Base-case cost-effectiveness analysis results.

Subgroups and strategies	Total population		Hormone receptor–positive cohort	
	T-DXd	Chemotherapy	T-DXd	Chemotherapy
Costs ($)				
PFS state ($)	123,002.03	15,022.56	135,342.29	16,255.62
PD state ($)	22,885.55	26,696.72	20,636.88	21,514.07
Total Cost ($)	145,887.58	41,719.28	155,979.16	37,769.70
Incremental costs ($)	104,168.30		118,209.46	
Effectiveness (QALYs)				
PFS state (QALYs)	0.96	0.55	1.08	0.63
PD state (QALYs)	0.61	0.71	0.55	0.57
Total effectiveness (QALYs)	1.57	1.26	1.63	1.20
Incremental effectiveness (QALYs)	0.31		0.43	
ICERs compared with PC alone ($/QALY)	336,026.77		274,905.72	

ICER, Incremental Cost Effectiveness Ratios; PD, progressive disease; PFS, Progression-Free Survival; QALY, Quality-adjusted Life Year; T-DXd, Trastuzumab Deruxtecan.

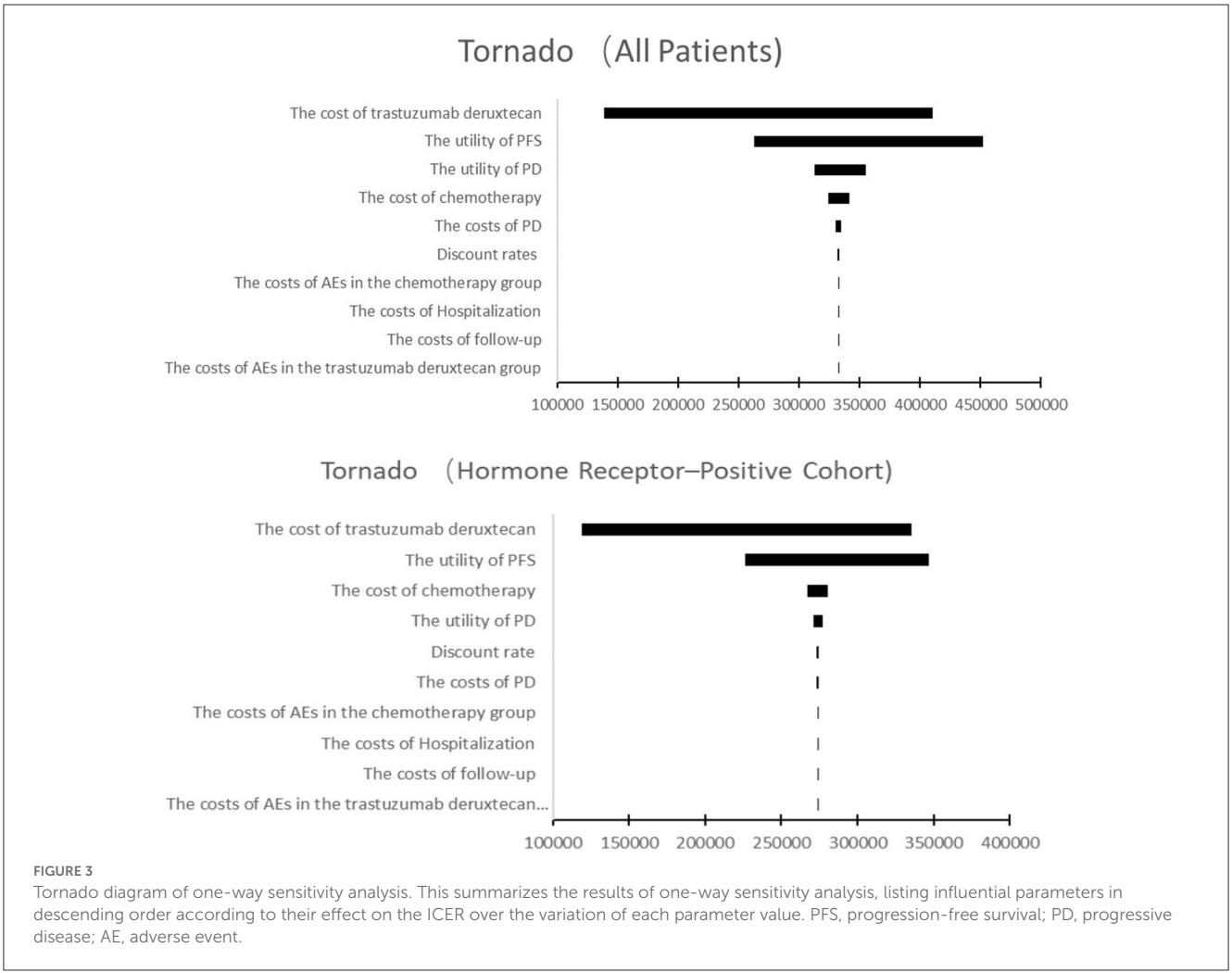

FIGURE 3
Tornado diagram of one-way sensitivity analysis. This summarizes the results of one-way sensitivity analysis, listing influential parameters in descending order according to their effect on the ICER over the variation of each parameter value. PFS, progression-free survival; PD, progressive disease; AE, adverse event.

with conventional WTP (34). At present, there is lack of effective treatment for HER2-low metastatic breast cancer refractory to standard treatment. The expected survival of these patients is <24 months, and T-Dxd could extend their survival time by more than 3 months comparing to single-agent chemotherapy. Therefore, we chose a high WTP threshold based on the NICE standard. But

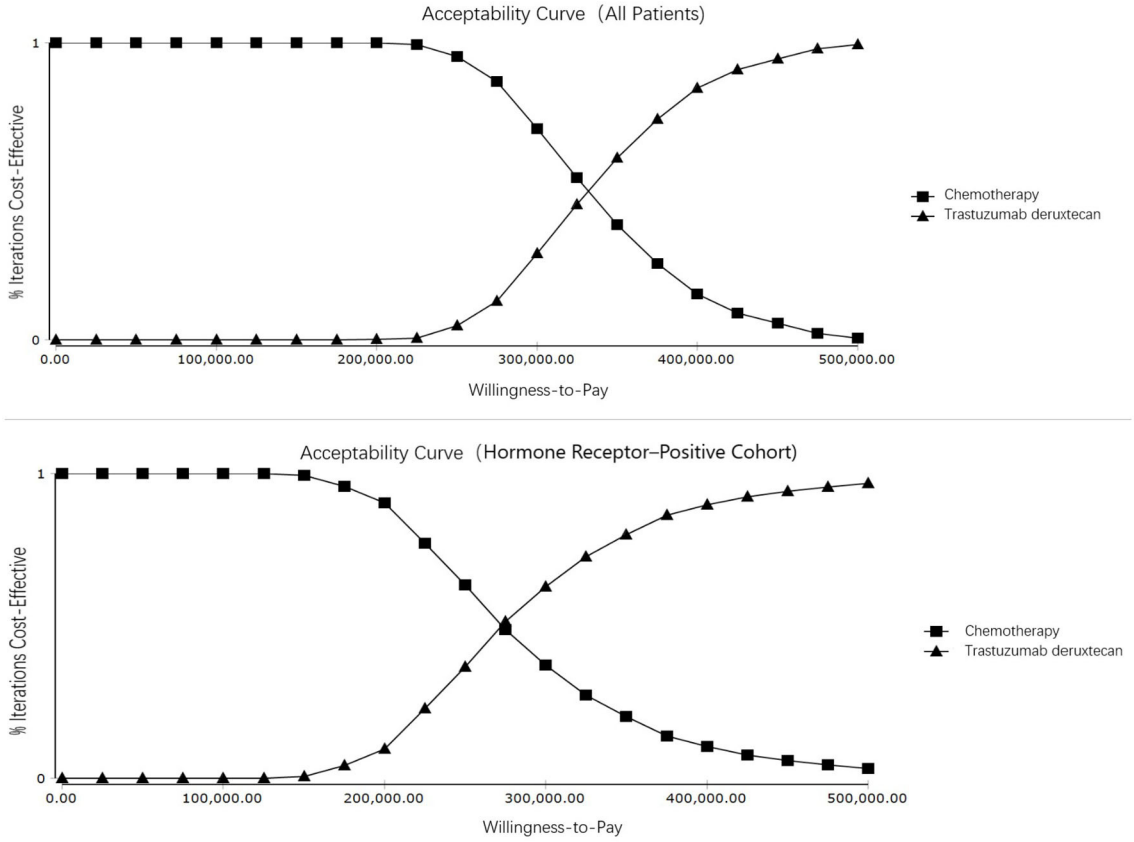

FIGURE 4
Cost-effectiveness acceptability curves. Cost-effectiveness acceptability curves show the probability of each treatment strategy being cost-effective at different willingness-to-pay thresholds.

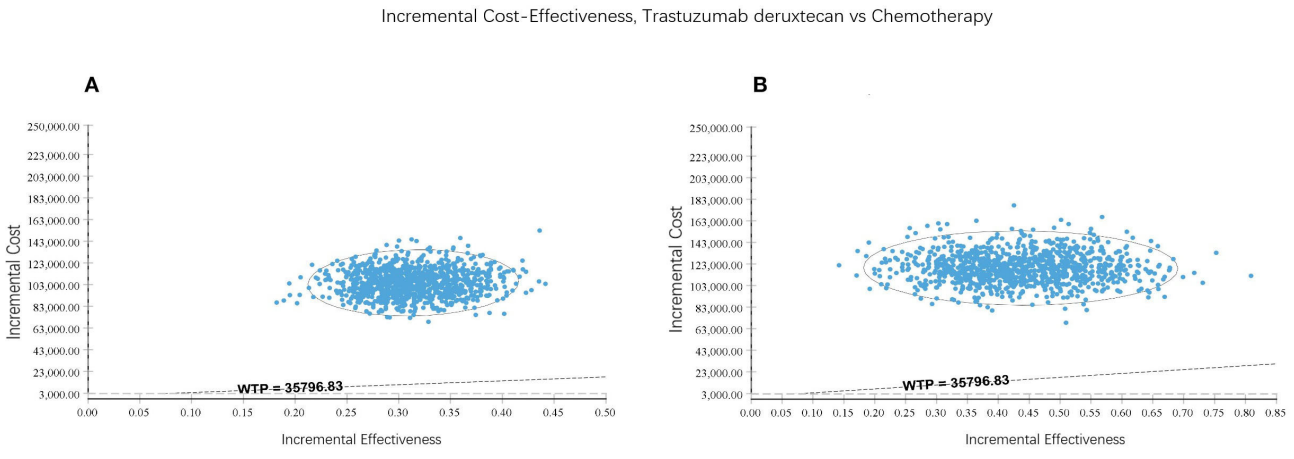

FIGURE 5
Incremental cost-effectiveness scatter plot reflected the variation and concentration of the incremental cost-effectiveness ratio values in probabilistic sensitivity analysis. **(A)** All patients. **(B)** Hormone receptor-positive cohort.

even if a high WTP is set, the results of this study showed that T-Dxd is still not cost-effective. Additionally, due to a series of new policies such as national centralized drug procurement and national medical insurance negotiations, the prices of anti-cancer drugs in China have greatly reduced in recent years. Therefore, in addition to the predicted price reduction of T-Dxd, the cost of alternative chemotherapy is also expected to decline, which may trigger the ICER to increase even higher. The results of PSA demonstrated that T-Dxd had no chance in practice to be cost-effective at the current payment threshold in China.

There are some limitations with this model-based cost-effectiveness analysis. Imprecise estimates and assumptions were made where it was necessary. First, the one-way sensitivity analysis showed the assumed cost of T-Dxd had significant impact on the results, but the T-Dxd price may drastically fluctuate in the next few years upon national approval. Secondly, DESTINY-Breast04 did not provide the information about the utility scores of the PFS and PD, thus the utility value referenced in this study was not based on Chinese population. Moreover, DESTINY-Breast04 only reported the AE rates for all patients. We hypothesized that the AE incidences were similar among the hormone receptor–positive cohort and all patients, thereby the cost of AEs was estimated based on the AE incidences of all patients. As of December 2022, T-Dxd has not yet been approved for marketing in Chinese mainland; therefore, we performed model-based cost-effectiveness analyses based on the RCT DESTINY-Breast04, the results of which may deviate from real world experience. As a result, imprecise estimates and assumptions were inevitable. The robustness was measured using sensitivity analysis and the results of sensitivity analyses showed that the results were stable.

In conclusion, although T-Dxd in previously treated HER2-low advanced breast cancer showed excellent clinical efficacy, the results of our study suggested that T-Dxd, comparing with single agent chemotherapy, was not cost effective from the perspective of the Chinese healthcare system. Another drug of the ADC class called T-DM1 proactively reduced its price by 50% after T-Dxd filed its application for marketing, therefore T-Dxd may need to mark down its price by a huge degree to appear cost-effective.

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.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Data curation: MZ, ZH, and HZ. Formal analysis: MZ, XX, and FW. Methodology: TX and FW. Writing—original draft: MZ and ZH. Writing—review and editing: FW. All authors contributed to the article and approved the submitted version.

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.

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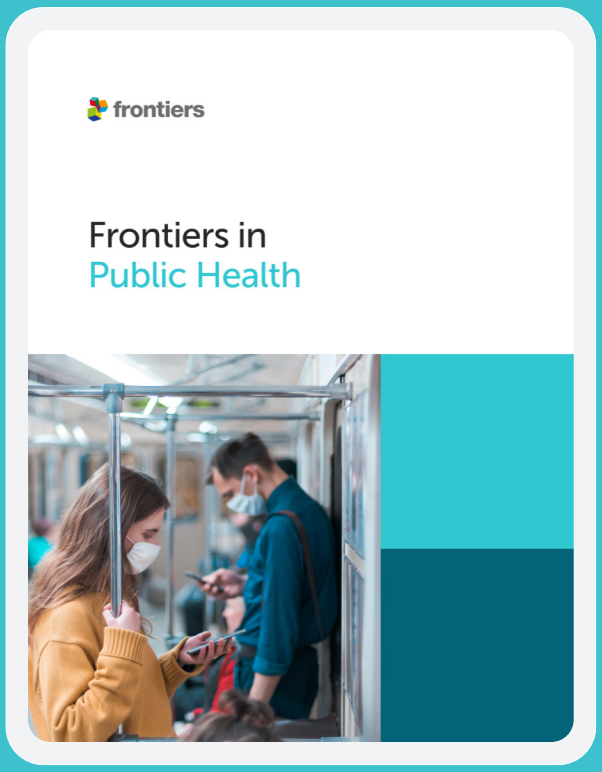

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