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Review Article

THE CLINICAL EFFECTIVENESS OF ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER: A SYSTEMATIC REVIEW

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Abstract: *Lung cancer imposes a significant epidemiological and economic burden globally, ranking second in incidence and first in mortality among all cancers. The rapid introduction of new, high-cost treatment options has placed substantial financial pressure on public healthcare systems. Given the limited healthcare resources, the economic evaluation of new cancer therapies is essential to ensure healthcare system sustainability and improve patient access to treatments. This study systematically reviews health state utility values (HSUVs) associated with traditional chemotherapy and targeted therapies in the first-line treatment of advanced or metastatic non-small cell lung cancer (NSCLC). A comprehensive search of the PubMed, EMBASE, and BioMed Central databases identified 10 studies from a total of 1,319 publications based on predefined inclusion criteria. The review reveals that HSUVs for targeted therapies are consistently higher across all health states compared to traditional chemotherapy. These findings provide a comprehensive framework for incorporating HSUVs into economic evaluations of NSCLC treatments and highlight the need for further empirical research to expand the range of available HSUVs.*

Keywords: *Non-Small Cell Lung Cancer, Health State Utility Values, Health-Related Quality of Life, Chemotherapy, Systematic Literature Review*

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1. Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide [1]. According to the Global Burden of Disease 2019 report, lung cancer ranks second in incidence and first in mortality among malignant tumors [2]. Non-small cell lung cancer (NSCLC), the most common subtype, accounts for approximately 85% of all lung cancer diagnoses [3]. NSCLC is often asymptomatic in its early stages, with two-thirds of patients being diagnosed at advanced or metastatic stages, resulting in a five-year survival rate of only 15% [4]. In advanced-stage cases where curative treatment or surgical intervention is not possible, chemotherapy can improve both patient survival and quality of life (QoL) [5].

Since the late 1990s, significant advancements have been made in cancer treatment, with platinum-based chemotherapies becoming the standard first-line treatment for NSCLC [6,7]. However, for advanced or metastatic NSCLC, overall survival (OS), progression-free survival (PFS), and progression survival (PD) rates achieved with chemotherapy are often suboptimal [8]. In the early 21st century, the development of targeted therapies significantly improved the prognosis of several cancers, including lung cancer. This shift has placed increasing emphasis on targeted therapies to enhance outcomes in advanced NSCLC [9,10]. These therapies are expected to reduce tumor size, regress

metastases, and alleviate some symptoms and systemic effects of the tumor, ultimately improving both QoL and survival rates [11]. However, the high cost of targeted therapies imposes a substantial economic burden, making their economic evaluation and reimbursement policies crucial [12]. Economic evaluations play a vital role in supporting evidence-based reimbursement decisions in cancer treatment [13].

The primary goals in treating advanced or metastatic NSCLC are to prolong survival and improve QoL [14]. A Quality-Adjusted Life Year (QALY) is a measure that captures the health gains provided by a medical intervention in terms of both life expectancy and quality of life [15,16]. In economic evaluation studies, health benefits are typically expressed in QALYs [17]. Health State Utility Values (HSUVs), fundamental to QALY calculations, allow for the quantitative assessment of QoL. HSUVs are numerical values that assess the quality of a specific health state, reflecting the desirability or preference for that health state [18,19]. QALYs are calculated by weighting the time spent in a particular health state according to its associated HSUVs, which are expressed as values ranging from 0 (representing death) to 1 (representing perfect health) [20]. Additionally, values lower than 0 can represent health states perceived as worse than death [21].

HSUVs are among the most uncertain yet critical input parameters in cost-utility analyses. Even small margins of error in their measurement can lead to significant deviations in QALYs and incremental cost-effectiveness ratios between compared treatments. Such deviations can potentially influence reimbursement and pricing decisions, thereby affecting the accessibility of an intervention [22].

HSUV measurement methods provide a means of quantifying how individuals assess various health states. These methods are typically divided into two main types: direct and indirect measurement methods [23,24,25]. The typology of HSUV measurement methods is presented in Table 1.

Table 1. Typology of HSUV Measurement Methods

<table>
<tr><th colspan="2">Preference-Based</th><th colspan="3">Non-Preference-Based</th></tr>
<tr><th>Direct Utility Assessment</th><th>Contingent Valuation</th><th colspan="3">Indirect Utility Assessment</th></tr>
<tr><td>The Time Trade-Off Method (TTO)</td><td rowspan="2">Willingness to Pay Method (WTP)</td><td>Generic HRQOL Instruments</td><td>Disease-Group Specific Instrument</td><td>Disease Specific Instruments</td></tr>
<tr><td>The Standard Gamble Method (SG)</td><td rowspan="3">EQ-5D, Health Utility Index (HUI), Short Form-6D (SF-6D), etc.</td><td rowspan="3">Patients Health Questionnaire-9 (PHQ-9), Dermatology Life Quality Index (DLQI)</td><td rowspan="3">Beck Depression Inventory (BDI), Hamilton Depression Scale (HADS), etc.</td></tr>
<tr><td>Discrete Choice Experiment (DCE)</td><td rowspan="2">Willingness to Accept Method (WTA)</td></tr>
<tr><td>Best-Worst Scaling (BWS)</td></tr>
</table>

Note: This typology does not list all measurement instruments.
Source: [25].

Direct measurement methods ask participants to choose between alternative health states, directly capturing their evaluations based on rational decision-making models [26]. These methods typically involve participants evaluating health states through scenarios or their current conditions. Common techniques include Standard Gamble (SG), Time Trade-Off (TTO), Discrete Choice Experiment (DCE), and Best-Worst Scaling (BWS) [25,26].

The most commonly used techniques for direct measurement of HSUVs are the SG and TTO methods [24]. SG assesses the choices individuals make between alternatives to determine which health states they value more. According to the rational decision-making model, when life expectancy is equal, individuals are expected to prefer the option leading to the best health outcome [27]. The TTO method evaluates the extent of life expectancy individuals are willing to sacrifice to live in a better health state [28]. For example, an individual might prefer to live 10 years in perfect health rather than 20 years in a specific health condition [27].

Indirect measurement methods, on the other hand, do not require patients to directly express their preferences for health states. Instead, these states are described using utility-based instruments, with scores assigned through predefined algorithms [29]. Depending on the research focus, different instruments may be used, including health-related quality of life (HRQOL) instruments such as EQ-5D and the Health Utilities Index (HUI), or disease-specific instruments like the Patient Health Questionnaire (PHQ-9) and the Dermatology Life Quality Index (DLQI) [25,29]. Indirect methods are often preferred in health policy decision-making due to their simplicity, speed, and ease of use [30].

Systematic reviews and meta-analyses of HSUVs provide a comprehensive framework for understanding choice-based utility values in lung cancer, enhancing the validity and reliability of future economic evaluations and guiding the use of HSUVs [31].

2. Methods

2.1. Study Objectives

This systematic literature review has two primary objectives: first, to systematically examine HSUVs associated with platinum-based chemotherapy in the first-line treatment of advanced or metastatic NSCLC; and second, to provide a comprehensive framework of HSUVs for use in pharmacoeconomic modeling of these treatments.

A systematic literature review is a comprehensive, organized, and repeatable process for selecting, evaluating, and summarizing existing knowledge from various databases based on predefined criteria to answer a research question. Systematic reviews and meta-analyses are increasingly important in health research and are widely used across many disciplines [32]. Several guidelines outline the rules for preparing systematic literature reviews [32,33]. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [32]. Additionally, the study followed the "Identification, Review, and Use of HSUVs in Cost-Effectiveness Models: An ISPOR Good Practices for Outcomes Research Task Force Report" [17], which serves as a methodological guide for health economics and outcomes research.

2.2. Data Sources and Search Strategy

In this study, HSUVs related to standard chemotherapy and targeted therapies in the treatment of advanced or metastatic NSCLC were examined. Studies published between January 1, 2000, and May 31, 2024, were reviewed. The databases used for identifying these studies included PubMed, EBSCO, and BioMed Central. Mendeley (version 1.19.8) and Rayyan, an intelligent systematic review tool [34], were used to prevent duplication, identify articles containing relevant keywords, and organize the data. Research sources were categorized based on topics and significance. The search strategy was adapted to align with the structure of the databases.

The search strategy used for the literature review is as follows:

(Advanced Non-Small Cell Lung Cancer OR Metastatic Non-Small Cell Lung Cancer OR Advanced NSCLC OR Metastatic NSCLC OR Advanced Lung Cancer OR Metastatic Lung Cancer OR Stage IV Lung Cancer) AND (First-Line Treatment OR First-Line Therapy OR Primary Treatment OR Initial Treatment OR Frontline Therapy) AND (Economic Evaluation OR Cost-Utility Analysis OR Cost-Effectiveness Analysis OR Health Economics OR Cost Analysis) AND (Platinum-Based Drugs OR Cisplatin OR Carboplatin OR Chemotherapy OR Targeted Therapy OR Immunotherapy)

2.3. Eligibility Criteria

This systematic literature review followed the Patient, Intervention, Comparator, and Outcome (PICO) framework, aligning with the research objectives. The inclusion and exclusion criteria are presented in Table 2.

The inclusion criteria focused on patients with advanced or metastatic NSCLC (stages IIIB-IV) who received first-line treatment. Studies addressing treatments for earlier stages were excluded. Eligible interventions and comparators included pharmacoeconomic evaluation studies involving platinum-based agents, chemotherapy, immunotherapy, and targeted therapies.

In advanced or metastatic NSCLC, a challenging cancer type with poor prognosis, surgical intervention is often not an option. Therefore, economic evaluation studies that clearly specify HSUVs based on active substances and progression levels were selected as the outcome criteria. After removing duplicates from the database searches, studies were screened by titles, abstracts, and HSUV characteristics. Only full-text pharmacoeconomic studies focusing on treatment regimens were included. Conference abstracts, reviews, editorials, notes, comments, letters, systematic reviews, and studies providing general HSUV/HRQoL data were excluded. Full-text articles that were inaccessible were also excluded.

Table 2. Inclusion and Exclusion Criteria

Criteria	Include	Exclude
Population	• Patients with advanced or metastatic stage NSCLC (stage IIIB-IV) • First-line Treatment	• Early-stage NSCLC patients (suitable for surgery; stages 0/I/II/III) • Pediatric patient population • Mixed disease populations where NSCLC data are not reported separately, • Patients receiving treatments other than first-line therapy
Intervention and Comparators	• Studies comparing treatment alternatives • Platinum-Based Drugs • Chemotherapy • Targeted Therapy • Immunotherapy	• Studies comparing diagnostic and screening alternatives • Standard monotherapies involving platinum-based treatment
Outcomes	• Direct and indirect HSUVs	• Health outcomes other than HSUVs • Disease-specific/general HSUV/HRQoL studies • Utility values not associated with a specific health state
Study Design	• Pharmacoeconomic evaluations • Studies with clearly defined health states (e.g., stable, progression, etc.) • Full-text research articles • Studies on treatment topics • Studies where HSUVs are specified according to health states and active substances.	• Conference papers • Reviews • Editorials • Notes/Comments/Letters • Systematic reviews
Publication Date	• January 1, 2000, to May 31, 2024	
Language	• English and Turkish	

2.4. Data Extraction and Quality Assessment

Study selection and data extraction were conducted by one analyst, with data elements verified by a second analyst. Decisions regarding data selection and extraction were made by one researcher and cross-checked by another. Using the Rayyan Intelligent Systematic Review tool, studies obtained after removing duplicate articles underwent processes including an overview, data review, screening, and full-text screening.

The collected study data were analyzed based on author, year, perspective, targeted therapy, treatments and doses, health states, HSUVs, and methods. Articles meeting the inclusion criteria were organized into Microsoft Excel tables. Eligibility assessments were conducted in accordance with the inclusion and exclusion criteria for each study. For methodological quality assessment, the checklist developed by Papaioannou et al. [35] was employed, focusing on the evaluation and quality of HSUVs.

3. Results

In this systematic literature review, economic evaluation studies involving dual platinum combination therapy as a first-line treatment in advanced or metastatic stages were identified using a predetermined search strategy, resulting in a total of 1,319 articles from all databases. After removing duplicate articles, the titles and abstracts of 842 articles were screened. Subsequently, 210 articles were selected for full-text evaluation to assess their eligibility based on inclusion and exclusion criteria. As a result of this assessment, the full texts of 10 studies were thoroughly reviewed and deemed appropriate for inclusion in the systematic review. No studies in the Turkish language meeting the criteria were identified.

The PRISMA flow diagram, which shows the study selection process and reasons for exclusion, is presented in Figure 1.

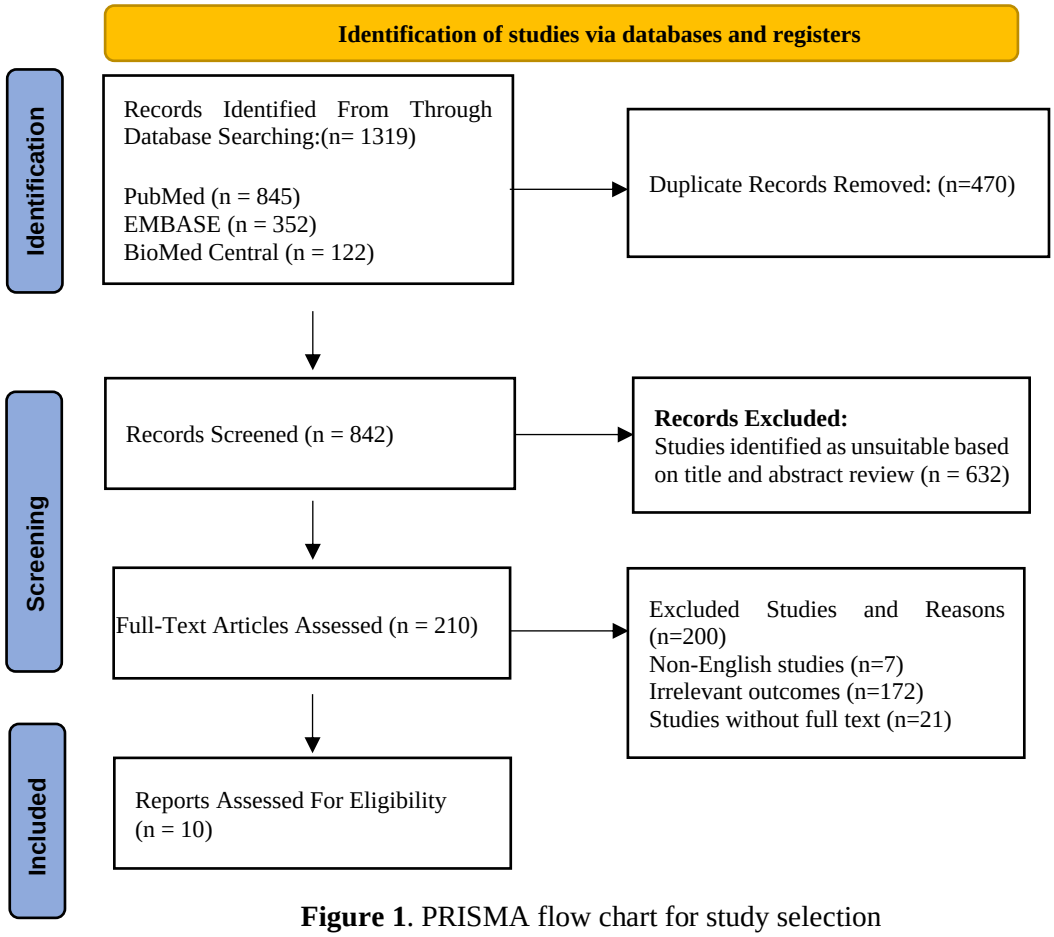

Figure 1. PRISMA flow chart for study selection

The findings related to the author, year, perspective, targeted therapy, treatments and doses, health states, HSUVs, and methods from the studies included according to the research criteria are presented in Table 3.

In this systematic literature review, five studies focused on the U.S. healthcare perspective [36, 40, 41, 43, 44]. There is one study each focusing on the healthcare systems of Turkey [38], Colombia [42], China [37], Ireland [45], and Thailand [39]. Additionally, one of the included studies reports from

both the U.S. and Taiwan healthcare perspectives [34]. A large portion of the included studies consists of comparisons between targeted therapies and standard chemotherapy treatments. However, it is noteworthy that only studies addressing EGFR and PD-L1 biomarkers met the inclusion criteria. In the systematic literature review, seven studies [37, 39, 40, 41, 43, 44, 45] focused on the cost-effectiveness analysis of targeted therapies, while three studies [36, 38, 42] concentrated on standard chemotherapy treatments. Although researchers have primarily focused on pharmacoeconomic comparisons of targeted therapies, standard chemotherapy treatments continue to hold significant importance.

According to HSUV measurement methods, Yalçın Balçık and Bayram [38] and Limwattananon et al. [39] obtained HSUVs using the EQ-5D scale. This method aims to directly determine the health state utility values from patients. In the other seven studies, HSUVs were adapted or transferred from similar pharmacoeconomic evaluation studies or disease-specific HSUV/HRQoL studies in the literature [36, 37, 40, 41, 42, 43, 44]. Additionally, in the study by She et al. [40], QLQ-C30 scores were mapped to the EQ-5D scale.

The combined use of direct and indirect measurement methods results in more comprehensive and balanced outcomes. Consequently, many studies have adapted HSUVs obtained through various methods. In Klein et al.'s study [36], the cost-effectiveness of cisplatin/pemetrexed, cisplatin/gemcitabine, carboplatin/paclitaxel, and carboplatin/paclitaxel/bevacizumab combinations was compared. HSUVs were derived using an algorithm developed by Nafees et al. [46], based on VAS scores, SG, and EQ-5D values. In Wang et al.'s study [37], the cost-effectiveness of erlotinib monotherapy versus Carboplatin + Gemcitabine combination in EGFR mutation-positive patients was analyzed. HSUVs were determined based on the progression levels described in studies by Nafees et al. [46] and Carlson et al. [47], using SG, VAS, and EQ-5D scales.

In the study by Hu et al. [41], a cost-effectiveness analysis was conducted comparing nivolumab and ipilimumab combination therapy with standard chemotherapy (pemetrexed + cisplatin/carboplatin) in patients with PD-L1 expression levels of ≥ 1% and < 1%. HSUVs were adapted based on progression status using algorithms reported by Nafees et al. [46] and Reck et al. [48], incorporating SG, EQ-5D, and VAS values. In the study by Wang et al. [44], cemiplimab was compared with platinum-based chemotherapy (pemetrexed, cisplatin, or carboplatin combinations) in patients with PD-L1 expression levels of at least 50%. This study used the adaptation method from Hu et al. [41], applying SG, EQ-5D, and VAS values.

The study conducted by Parody Rua et al. [42] compares the cost-effectiveness of Carboplatin + Paclitaxel versus Carboplatin + Paclitaxel + Bevacizumab combinations. The health states are defined as PFS, progression, and terminal stage. The utility values used in the study were obtained from various studies in the literature and international databases, including those by Nafees et al. [46], Chouaid et al. [49], and the Tufts Medical Center CEA (Cost-Effectiveness Analysis) database [50].

In the study by Yang et al. [43], the cost-effectiveness of nivolumab + ipilimumab or nivolumab + ipilimumab + standard chemotherapy was compared in patients with PD-L1 tumor proportion scores of ≥1% and <1%. HSUV values were adapted using EQ-5D and WHOQOL-BREF scores from the CheckMate 9LA and CheckMate 227 phase 3 trials conducted by Yang et al. [51] and Reck et al. [48], respectively.

In the study by She et al. [40], cost-effectiveness analyses were conducted comparing pembrolizumab with standard chemotherapy in patients with tumor proportion scores of ≥50%, ≥20%, and ≥1%. Utility values were mapped from QLQ-C30 scores to EQ-5D utility values using algorithms published from the KEYNOTE-024 study [52], facilitating the economic evaluation of treatment options. Similarly, in the study by Chu et al. [45], a cost-effectiveness analysis was conducted comparing pembrolizumab monotherapy with chemotherapy in patients with PD-L1 tumor proportion scores of 50% or higher. Health State Utility Values (HSUVs) were also adapted from the randomized study in the KEYNOTE-024 trial [52]

Table 3. HSUVs in Targeted and Standard Therapies for Advanced or Metastatic NSCLC

Authors	Perpective	Biomarker Status	Treatment Regimen	HSUV Values	Measurement Method
Klein et al. [36]	U.S. Payer Perspective.	-	**Platinum-Based Chemotherapy Regimens Among** • Cisplatin: 75 mg/m² Q3W IV • Pemetrexed: 500 mg/m² Q3W IV • Gemcitabine: 1250 mg/m² D1, D8 Q3W IV • Carboplatin: AUC 6 Q3W IV • Paclitaxel: 200 mg/m² Q3W IV • Bevacizumab: 15 mg/kg Q3W IV	**Progressive Disease:** No Treatment: 0.47 Mild Side Effects (Cis/Pem): 0.48 Mild Side Effects (Cis/Gem): 0.48 Mild Side Effects (Carb/Pac): 0.48 Mild Side Effects (Carb/Pac/Bev): 0.48 Serious Side Effects: 0.31 **Stable Disease:** No Treatment: 0.65 Mild Side Effects (Cis/Pem): 0.56 Mild Side Effects (Cis/Gem): 0.56 Mild Side Effects (Carb/Pac): 0.56 Mild Side Effects (Carb/Pac/Bev): 0.56 Serious Side Effects: 0.49 **Partial Response:** No Treatment: 0.67 Mild Side Effects (Cis/Pem): 0.58 Mild Side Effects (Cis/Gem): 0.58 Mild Side Effects (Carb/Pac): 0.58 Mild Side Effects (Carb/Pac/Bev): 0.58 Serious Side Effects: 0.51 **Complete Response:** No Treatment: 0.85 Mild Side Effects (Cis/Pem): 0.75 Mild Side Effects (Cis/Gem): 0.75 Mild Side Effects (Carb/Pac): 0.75 Mild Side Effects (Carb/Pac/Bev): 0.75 Serious Side Effects: 0.68 **End of Life:** No Treatment: 0.35 Mild Side Effects (Cis/Pem): 0.25 Mild Side Effects (Cis/Gem): 0.25 Mild Side Effects (Carb/Pac): 0.25 Mild Side Effects (Carb/Pac/Bev): 0.25	Based on the VAS scores, SG, and EQ-5D values reported by Nafees et al. [46], utility values were adapted.

Authors	Perpective	Biomarker Status	Treatment Regimen	HSUV Values	Measurement Method
				Serious Side Effects: 0.18	
Wang et al. [37]	Chinese Healthcare System Perspective	EGFR +	**Erlotinib vs. Chemotherapy** • **Target Treatment:** • Erlotinib: 150 mg/day oral • **Alternative Agents (Chemotherapy):** • Carboplatin: AUC 5 Q3W IV • Gemcitabine: 1000 mg/m² Q1W IV	**Progression-Free Survival:** Erlotinib: 0.65 (Range: 0.26–0.87) CG (Carboplatin + Gemcitabine): 0.56 (Range: 0.224–0.75) **Disease Progression:** General: 0.47 (Range: 0.30–0.58)	Based on the algorithms reported by Nafees et al. [46] and Carlson et al. [47], which mapped VAS scores, SG, and EQ-5D values to utility values.
Yalçın Balçık and Bayram [38]	Turkish Social Security Institution (SGK) perspective	-	**Platinum-Based Chemotherapy Regimens Among** • Pemetrexed: 500 mg/m² Q3W IV • Cisplatin: 75 mg/m² Q3W IV • Gemcitabine: 1250 mg/m² Q1W IV	**Progression-Free Survival:** Cisplatin + Gemcitabine: 0.70 Cisplatin + Pemetrexed: 0.82 **Progressive Disease:** Cisplatin + Gemcitabine: 0.63 Cisplatin + Pemetrexed: 0.64	Empirically, HSUV values were obtained by applying the EQ-5D scale.
Limwattananon et al. [39]	Thailand healthcare system perspective	EGFR	**Target Treatment:** • Gefitinib: 250 mg/day oral • Erlotinib: 150 mg/day oral • Afatinib: 40 mg/day oral **Alternative Agents (Chemotherapy):** • Carboplatin: AUC 5-6 Q3W IV • Paclitaxel: 200 mg/m² Q3W IV • Cisplatin: 75 mg/m² Q3W IV • Gemcitabine: 1250 mg/m² Q1W IV	Use of platinum doublets 0.54 (0.48-0.60) Use of Tyrosine kinase inhibitors: 0.67 (0.59-0.77) No progression 0.68 (0.62-0.74) Disease progression 0.32 (0.07-0.58)	Empirically, HSUV values were obtained by applying the EQ-5D scale.
She et al. [40]	U.S. Payer Perspective.	TPS ≥ %50, TPS ≥ %20 ve TPS ≥ %1	**Pembrolizumab vs. Platinum-Based Chemotherapy** **Target Treatment:** • Pembrolizumab: 200 mg Q3W IV **Alternative Agents (Chemotherapy):** • Carboplatin: AUC 5-6 Q3W IV • Paclitaxel: 200 mg/m² Q3W IV	**Progression-Free Survival:** Pembrolizumab: 0.691 (Range: 0.5582–0.8292) Chemotherapy: 0.653 (Range: 0.5224–0.7863) **Progressive Disease:** General: 0.473 (Range: 0.3784–0.5676)	The QLQ-C30 scores applied in the KEYNOTE-024 study [52] were mapped based on utility values

Authors	Perpective	Biomarker Status	Treatment Regimen	HSUV Values	Measurement Method
			• Pemetrexed: 500 mg/m² Q3W IV		
Hu et al. [41]	U.S. Payer Perspective.	PD-L1 (≥50, ≥1, and <1%)	**Nivolumab+ Ipilimumab vs. Platinum-Based Chemotherapy** • **Target Treatment:** • Nivolumab: 3 mg/kg Q2W IV • İpilimumab: 1 mg/kg Q6W IV **Alternative Agents (Chemotherapy):** • Carboplatin: AUC 5 Q3W IV • Pemetrexed: 500 mg/m² Q3W IV • Paclitaxel: 200 mg/m² Q3W IV • Gemcitabine: 1000 mg/m² Q1W IV	**Progression-Free Survival:** Nivolumab plus Ipilimumab: 0.784 (Range: 0.74–0.828) Chemotherapy: 0.693 (Range: 0.642–0.743) **Progressive Disease:** General: 0.473 (Range: 0.166–0.568)	Based on the algorithms reported by Nafees et al. [46] and Reck et al. [48], VAS scores, SG, and EQ-5D values were mapped to utility values.
Parody-Rúa and Guevara-Cuellar [42]	Colombian healthcare system perspective	-	**Platinum-Based Chemotherapy Regimens Among** • Carboplatin+Paclitaxel Carboplatin+Paclitaxel+Bevacizumab	**Progression-Free Survival:** Carboplatin + Paclitaxel: 0.75 Bevacizumab + Carboplatin + Paclitaxel: 0.77 **Progressive Disease:** Carboplatin + Paclitaxel: 0.59 Bevacizumab + Carboplatin + Paclitaxel: 0.62	Based on the algorithms reported by Nafees et al. [46], Chouaid et al. [49], and the Tufts Medical Center [50], VAS scores, SG, and EQ-5D values were converted into utility values.
Yang et al. [43]	U.S. Payer Perspective.	PD-L1 ≥ %1 ve < %1	**Nivolumab+ Ipilimumab vs. Platinum-Based Chemotherapy** **Target Treatment:** • Nivolumab: 3 mg/kg Q2W IV • İpilimumab: 1 mg/kg Q6W IV **Alternative Agents (Chemotherapy):** • Carboplatin: AUC 5 Q3W IV	**Progression-Free Survival:** Nivolumab plus Ipilimumab with/without chemotherapy: 0.88 (Range: 0.79–0.97) Chemotherapy: 0.79 (Range: 0.71–0.87) **Progressive Disease:**	Based on utility values, the EQ-5D and WHOQOL-BREF scores obtained from the CheckMate 227 [48] and

Authors	Perpective	Biomarker Status	Treatment Regimen	HSUV Values	Measurement Method
			• Pemetrexed: 500 mg/m² Q3W IV • Paclitaxel: 200 mg/m² Q3W IV • Gemcitabine: 1000 mg/m² Q1W IV	General: 0.72 (Range: 0.65–0.79)	CheckMate 9LA [51] phase 3 randomized trials were mapped.
Wang et al. [44]	U.S. Payer Perspective.	PD-L1≥50	**Cemiplimab vs. Standard Chemotherapy** **Target Treatment:** Cemiplimab: 350 mg Q3W IV **Alternative Agents (Chemotherapy):** • Pemetreksed: 500 mg/m² Q3W IV • Sisplatin: 75 mg/m² Q3W IV • Sisplatin: 100 mg/m² Q3W IV • Karboplatin: AUC 5-6 Q3W IV • Paklitaksel: 200 mg/m² Q3W IV • Gemsitabin: 1250 mg/m² Q1W IV	**Progression-Free Survival:** Cemiplimab: 0.784 (Range: 0.627–0.940) Chemotherapy: 0.693 (Range: 0.554–0.831) **Progressive Disease:** General: 0.473 (Range: 0.3784–0.5676)	Using the example from the study by Hu et al. [41], the algorithms reported by Nafees et al. [46] and Reck et al. [48] were used to map VAS scores, SG, and EQ-5D values to utility values.
Chu et al. [45]	Irish Healthcare System Perspective	PD-L1 ≥%50	**Pembrolizumab vs. Chemotherapy** **Target Treatment:** Pembrolizumab: 200 mg Q3W IV **Alternative Agents (Chemotherapy):** • Pemetreksed: 500 mg/m² Q3W IV • Paklitaksel: 200 mg/m² Q3W IV • Karboplatin: AUC 5-6 Q3W IV • Sisplatin: 75 mg/m² Q3W IV • Gemsitabin: 1250 mg/m² Q1W IV	**Progression-Free Survival:** Pembrolizumab: 0.808 Chemotherapy: 0.757 **Progressive Disease:** Pembrolizumab: 0.737 Chemotherapy: 0.687	The QLQ-C30 scores applied in the KEYNOTE-024 study [52] were mapped based on utility values

In the studies conducted by Yalçın Balçık and Bayram [38] and Klein et al. [37], the cost-effectiveness of cisplatin+pemetrexed versus cisplatin+gemcitabine was compared. The mean HSUV values for the cisplatin+gemcitabine combination were reported as 0.63 (0.599 – 0.662) for PFS and 0.556 (0.532 – 0.588) for PD. For the cisplatin+pemetrexed combination, the mean values were 0.688 (0.656 – 0.724) for PFS and 0.559 (0.532 – 0.588) for PD. Additionally, Klein et al. [37] included comparisons with carboplatin+paclitaxel and carboplatin+paclitaxel+bevacizumab combinations. In the study by Parody-Rúa and Guevara-Cuellar [42], the average HSUV values for the carboplatin+paclitaxel combination were 0.655 (0.622 – 0.688) for PFS and 0.475 (0.451 – 0.499) for PD.

Hu et al. [41] and Yang et al. [43] compared the Nivolumab+Ipilimumab combination with standard platinum-based chemotherapy, finding that the Nivolumab+Ipilimumab combination had higher HSUV values. The average values were 0.832 (0.790 – 0.873) for PFS and 0.596 (0.566 – 0.626) for PD, compared to 0.741 (0.704 – 0.778) for PFS with standard chemotherapy. She et al. [40] and Chu et al. [45] compared Pembrolizumab monotherapy with standard platinum-based chemotherapy. The average HSUV values for Pembrolizumab monotherapy were 0.749 (0.712 – 0.787) for PFS and 0.605 (0.574 – 0.635) for PD. For standard chemotherapy, these values were 0.705 (0.669 – 0.740) for PFS and 0.58 (0.551 – 0.609) for PD.

In Wang et al. [44], the HSUV values for cemiplimab monotherapy were reported as 0.784 (0.627–0.940) for PFS, while for standard platinum-based chemotherapy, they were 0.693 (0.554–0.831) for PFS and 0.473 (0.378–0.567) for PD. Limwattananon et al. [39] and Wang et al. [37] found that erlotinib monotherapy had higher HSUV values compared to standard platinum-based chemotherapy, with average HSUV values of 0.66 (0.627 – 0.693) for PFS and 0.395 (0.375 – 0.415) for PD. These studies indicate that targeted therapies generally have higher utility values compared to standard platinum-based chemotherapy.

Table 4. The Average HSUVs For Standard Chemotherapy And Targeted Therapies

Treatment Combination	PFS HSUV (Range)	PD HSUV (Range)
Cisplatin+Gemcitabine	0,63 (0,599 – 0,662)	0,556 (0,532 – 0,588)
Cisplatin+Pemetrexed	0,688 (0,656 – 0,724)	0,559 (0,532 – 0,588)
Carboplatin+Paclitaxel	0,655 (0,622 - 0,688)	0,475 (0,451 - 0,499)
Nivolumab+Ipilimumab	0,832 (0,790 – 0,873)	0,596 (0,566 – 0,626)
Pembrolizumab Monotherapy	0,749 (0,712 – 0,787)	0,605 (0,574 – 0,635)
Cemiplimab Monotherapy	0,784 (0,627-0,940)	0,473 (0,378-0,567)
Erlotinib Monotherapy	0,66 (0,627 – 0,693)	0,395 (0,375 – 0,415)

The HSUVs for chemotherapy and targeted therapy regimens used in the treatment of advanced or metastatic NSCLC, derived from studies meeting the inclusion criteria, are presented in Table 4. The HSUVs are evaluated for PFS and PD states, with their averages and 5% margins of error used to calculate the lower and upper limits. This table allows for a comparative analysis of the utility values across different therapeutic agents and provides data for economic evaluation studies.

4. Conclusion

This systematic literature review aims to provide a comprehensive analysis of HSUVs for platinum-based chemotherapy and targeted therapies in the treatment of advanced or metastatic NSCLC.

In situations where healthcare resources are limited, their allocation is not based solely on economic evaluations; the expertise and knowledge of healthcare professionals are also crucial. It is important to evaluate a wide range of studies in health economics and achieve common conclusions through objective, high-quality analyses. Systematic literature reviews enable a more comprehensive approach to health economics and policy decisions.

Comparing HSUVs for targeted therapies with those for standard platinum-based chemotherapy in advanced or metastatic NSCLC suggests that targeted therapies offer higher scores for both PFS and PD, indicating the potential for improved quality of life and extended survival compared to standard chemotherapies.

HSUVs are crucial components used in economic evaluations to calculate QALYs. The findings indicate that most HSUVs used in cost-effectiveness analyses of different treatment regimens are derived from disease-specific HSUV/HRQoL studies in the literature. Data obtained through empirical methods reflect patients' quality of life more directly, while HSUVs adapted from the literature provide broader applicability. HSUVs from different studies and methods are essential for data diversity, broad comparisons, and obtaining valid results in pharmacoeconomic research.

In developing countries such as Turkey, there is a shortage of pharmacoeconomic evaluations and systematic reviews related to cancer. Therefore, more studies are needed to provide reliable data for cost-effectiveness analyses. Increasing both the quality and quantity of these studies will help ensure better healthcare decisions for patients.

This systematic literature review aims to provide reliable HSUV estimates for use in economic evaluations of platinum-based treatments in advanced or metastatic NSCLC. Our study emphasizes that targeted therapies offer higher HSUVs for both PFS and PD, indicating a potential for better quality of life compared to standard chemotherapies.

Ethical Statement:

This paper is exempt from the Institutional Ethics Committee review since it does not involve human subjects.

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Conflict of interest:

There is no conflict of interest to declare.

Authors' Contributions:

Both authors collaborated on the research processes, including data acquisition, overview, data review, screening, and full-text screening.

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