

Economic Burden, Utilities, and Cost-Effectiveness of Perioperative Immunotherapies for Early-Stage Non-Small Cell Lung Cancer: A Systematic Literature Review

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CONCLUSIONS

- The economic burden of early-stage NSCLC is substantial, with significant financial costs associated with perioperative treatment that increase with advancing disease stage
- Immunotherapy treatments consistently showed clinical benefits across various settings, but were associated with higher costs, leading to varying cost-effectiveness results based on local pricing and healthcare systems
- Despite high treatment costs, many economic evaluations found that immunotherapy has the potential to be cost-effective or cost-saving
- Key drivers of cost-effectiveness identified were clinical effectiveness, time to immunotherapy rechallenge after recurrence, disease-free survival rates, transition probabilities, quality of life, treatment costs, duration of treatment effect, HCRU inputs such as the probability of hospitalization and the average number of doctor visits, PD-L1 status, discount rates, utility values, and survival benefits
- The review identified gaps in consistent reporting, geographic representation, and the inclusion of indirect and societal costs

INTRODUCTION

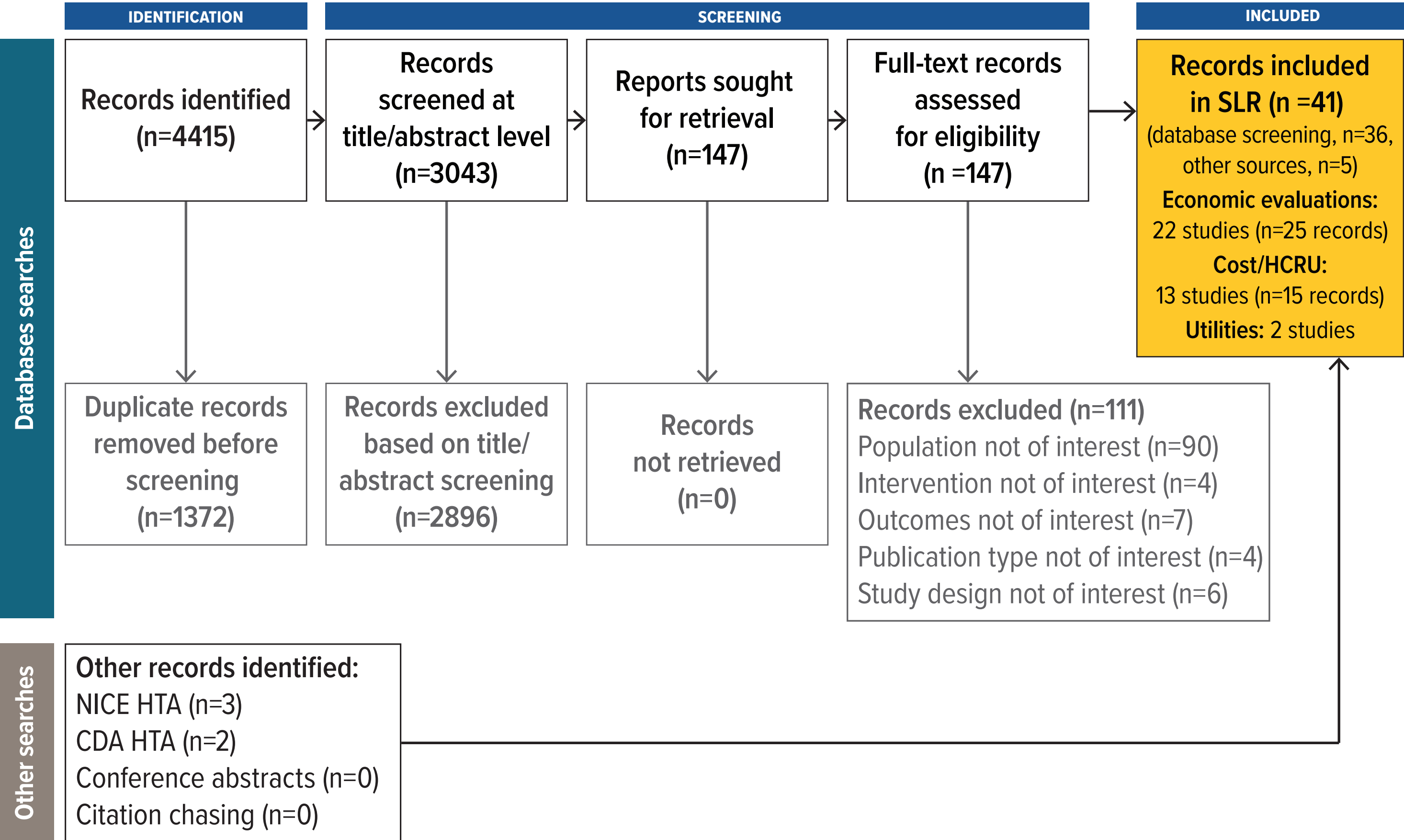
- Early-stage non-small cell lung cancer (NSCLC; resectable, stage II-IIIA NSCLC) represents a significant portion of lung cancer diagnoses, with patients being candidates for perioperative systemic therapies
- Perioperative systemic treatments, covering both neoadjuvant (pre-surgical) and adjuvant (post-surgical) therapies, aim to improve outcomes in early-stage, resectable NSCLC.¹ Neoadjuvant treatments are intended to reduce tumor size, making surgery more feasible and potentially more effective, while adjuvant treatments seek to eliminate residual microscopic disease, thereby minimizing the risk of recurrence
- Immunotherapy treatments have demonstrated clinical benefits for early-stage NSCLC across multiple treatment settings. However, high costs continue to be a central issue, leading to variations in cost-effectiveness results depending on local drug pricing and healthcare systems
- The aim of this review is to systematically collate evidence on economic evaluations, costs, resource use, and utilities associated with current systemic therapies for perioperative treatment of early-stage NSCLC

METHODS

- The systematic literature review (SLR) was conducted according to the standards set forth in the Cochrane Handbook for Systematic Reviews of Interventions, as well as the high-quality standards required by the National Institute for Health and Care Excellence (NICE)
- Searches were conducted on September 18, 2024, in MEDLINE, MEDLINE In-Process, Embase, Cochrane Central Register of Controlled Trials, National Health Service Economic Evaluation Database, EconLit, and PsychINFO. The search was limited to studies from the start of 2013 to September 18, 2024, and supplemented with grey literature searches conducted in September 2024 across conference proceedings from the past 2 years (2022-2024), health technology assessments (HTAs), and recently published SLRs (2021-2024)
- Articles were screened by two independent reviewers, with discrepancies resolved by a third reviewer

RESULTS

Figure 1 PRISMA Diagram



Abbreviations: CDA, Canada's Drug Agency; HCRU, healthcare resource utilization; HTA, health technology assessment; NICE, National Institute for Health and Care Excellence; SLR, systematic literature review.

- The database search retrieved 4415 records; after removing duplicates, 3043 titles and abstracts were screened, and 147 full texts were assessed for eligibility (**Figure 1**)
- Ultimately, 36 publications were included from the database searches and five HTA submissions identified through grey literature search were incorporated into the review. Therefore, in total, 41 publications were included in this SLR, comprising 22 economic evaluations (25 publications), 13 cost/healthcare resource utilization (HCRU) studies (15 publications), and two utilities studies
 - Most studies were conducted in the United States (US) and various European countries
 - Twelve were cost-effectiveness analyses, seven were cost-utility analyses, and three were budget impact analyses

Economic Evaluations

- Two studies evaluated pembrolizumab in the perioperative setting.^{2,3} The incremental cost-effectiveness ratio (ICER) in the US study was \$94,223 United States dollars (USD) per quality-adjusted life year (QALY) compared to neoadjuvant chemotherapy.³ The primary cost driver was the high cost of pembrolizumab treatment (price per milligram).³ The ICER in the United Kingdom (UK) was redacted from the NICE HTA appraisal, but was noted to be cost-effective versus traditional treatment options and likely to be cost-effective versus neoadjuvant nivolumab²
- Neoadjuvant nivolumab was a cost-effective strategy when compared to surgery alone or chemoradiotherapy across three studies conducted in the UK,⁴ the US,⁵ and Canada.⁶ Cost-effectiveness in the US was primarily influenced by the effectiveness of immunotherapy at recurrence and PD-L1 expression levels, with the lowest ICER observed when immunotherapy was effective at recurrence.⁵ Cost drivers included the high cost of nivolumab treatment, long-term treatment effectiveness, and patient access scheme adjustments
- While adjuvant atezolizumab demonstrated higher life years and QALYs compared to best supportive care (BSC) across 15 studies, the interpretation of ICERs varied depending on each country's cost-effectiveness thresholds. Two cost-effectiveness analyses conducted in China⁷ and the US⁵ and three budget impact analyses conducted in Italy,⁸ the US,⁹ and Canada¹⁰ found atezolizumab to be cost-saving versus BSC or active surveillance. Cost drivers included utilities, treatment costs, treatment effectiveness, and resource utilization

Direct and Indirect Costs

- Ten studies¹¹⁻²¹ reported data on total direct costs, highlighting significant financial burdens associated with perioperative NSCLC treatment. Costs increased with disease stage, largely driven by higher hospitalization costs. For example, a US-based study reported mean per-patient per-month costs of \$6622 USD for stage IIA, \$8307 USD for stage IIB, and \$9255 USD for stage IIIA¹¹
- Adjuvant therapy incurred higher median monthly costs in the US (2013 costs; \$17,496 USD for IIA, \$17,784 USD for IIB, and \$13,659 USD for IIIA) compared to mixed setting treatments (ranging from \$1368 USD to \$1714 USD)¹²
- Newly diagnosed US NSCLC patients receiving adjuvant/neoadjuvant therapy had lower costs (year of costs: 2020) than those undergoing surgery alone, with differences of \$1362 USD, \$857 USD, and \$1836 USD per month for stages IIA, IIB, and IIIA, respectively¹⁴
- Among patients in Italy receiving adjuvant chemotherapy, the mean annual cost per patient at 1 year was €23,607, decreasing to €9266 at 2 years and €10,004 at 3 years
- Data for indirect costs in patients treated with perioperative treatment for early-stage NSCLC were available in only one study conducted in France, Germany, and the UK. Indirect costs during adjuvant therapy averaged €372 (95% CI, €81-€749) per patient per month, including childcare (averaged €29) and travel-related costs (averaged €81)¹⁹
 - Across the three countries, employed patients reported a mean of 32 days of missed work over the past 3 months. Additionally, family members or unpaid caregivers missed an average of 14.7 days of work during the same period

Healthcare Resource Utilization

- HCRU data for the perioperative setting were available from nine studies^{11-13,17-19,21-23}
- Hospitalizations and emergency department visits were consistently higher in patients with advanced stages, or for those experiencing recurrence, with notable geographic variability. Outpatient visits and treatment utilization were also highest in the more advanced stages
- While general practitioner and specialist visits declined over time, HCRU remained elevated in recurrent cases

Utilities and Disutilities

- There was limited evidence from two studies reporting utilities in patients with early-stage NSCLC
- Among patients treated with adjuvant chemotherapy regimens in France, Germany, and the UK, the baseline EQ-5D utility score was higher for disease-free patients (0.72) compared to those with loco-regional recurrence (0.62)¹⁹
- Patients receiving neoadjuvant nivolumab plus chemotherapy in an RCT showed a slight improvement in utility scores at week 4, followed by declines at week 7 and post-neoadjuvant first visit²⁴
- Strengths and Limitations of the Evidence Base**
 - The high costs associated with immunotherapy treatments present a significant challenge, with cost-effectiveness results varying by local drug pricing and healthcare systems. Limitations in the included economic studies affect the interpretability of results and conclusions
 - The predominance of US and European studies restricts the applicability of findings to regions with different healthcare systems and cost structures. Database searches were not restricted by geographic region, but manual searches of HTAs were limited to six HTA agencies
 - Inconsistent reporting of key economic metrics, such as ICERs, hampers comparisons between studies
 - The absence of specific economic data in some studies (eg, redacted ICER values in the NICE HTA) limits the completeness of the review
 - The inclusion of diverse data sources—large databases, registries, trial data, published literature, and hospital records—enhances the robustness and reliability of findings on the economic burden of disease. However, the predominance of retrospective cohort studies may introduce biases inherent in retrospective data collection and analysis
 - The observed variability in utility scores and limited evidence from only two studies challenge the interpretation of long-term quality-of-life outcomes

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DISCLOSURES

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