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SYSTEMATIC REVIEW

Systematic Literature Review to Identify Cost and Resource Use Data in Patients with Early-Stage Non-small Cell Lung Cancer (NSCLC)

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Abstract

Background Approximately 2 million new cases and 1.76 million deaths occur annually due to lung cancer, with the main histological subtype being non-small cell lung cancer (NSCLC). The costs and resource use associated with NSCLC are important considerations to understand the economic impact imposed by the disease on patients, caregivers and healthcare services.

Objective The objective of this systematic literature review (SLR) is to provide a comprehensive overview of the available direct medical costs, direct non-medical costs, indirect costs, cost drivers and resource use data available for patients with early-stage NSCLC.

Methods Electronic searches were conducted via the Ovid platform in March 2021 and June 2022 and were supplemented by grey literature searches. Eligible patients had early-stage (stage I–III) resectable NSCLC and received treatment in the neoadjuvant or adjuvant setting. There was no restriction on intervention or comparators. Publication date was restricted to 2011 onwards, and English language publications or non-English language publications with an English abstract were of primary interest. Due to the anticipation of many studies meeting the inclusion criteria, analyses were restricted to full publications from countries of primary interest (Australia, Brazil, Canada, China, France, Germany, Italy, Japan, South Korea, Spain, UK and the US) and those with > 200 patients. The Molinier checklist was applied to conduct quality assessment.

Results Forty-two full publications met the eligibility criteria and were included in this SLR. Early-stage NSCLC was associated with significant direct medical costs and healthcare utilisation, and the economic burden of the disease increased with its progression. Surgery was the primary cost driver in stage I patients, but as patients progressed to stage II and III, treatments such as chemotherapy and radiotherapy, and inpatient care became the main cost drivers. There was no significant difference in resource use between patients with early-stage disease. However, these data were heavily US-centric and there was a paucity of data relating to direct non-medical and indirect costs associated with early-stage NSCLC.

Conclusions Preventing disease progression for patients with NSCLC could reduce the economic burden of NSCLC on patients, caregivers and healthcare systems. This review provides a comprehensive overview of the available cost and resource use data in this indication, which is important in guiding the decisions of policy makers regarding the allocation of resources. However, it also indicates a need for more studies comparing the economic impact of NSCLC in markets in addition to the US.

1 Introduction

Lung cancer remains one of the most frequently diagnosed cancers worldwide and is the leading cause of cancer-related deaths, with an estimated 2 million new cases and 1.76 million deaths per year [1, 2]. The most common type of lung cancer is non-small cell lung cancer (NSCLC), which represents 80–85% of all lung cancer cases [3]. Complete surgical resection is the recommended treatment for patients presenting with early-stage disease (stage I/II and stage

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Key Points for Decision Makers

The economic burden of early-stage non-small cell lung cancer (NSCLC) stems from significant healthcare resource utilisation and direct medical costs.

Direct medical costs increase with stage of disease, primarily driven by the change in treatment administered (surgery [stage I] versus chemotherapy [stage II/III]).

There is a paucity of published studies reporting direct non-medical and indirect costs; however, the systematic literature review provides a comprehensive overview of the available cost and resource use data associated with early-stage NSCLC.

IIIA NSCLC), followed by adjuvant chemotherapy [4–7]. However, the 5-year survival rate for these patients has been reported to range from 10 to 64%, indicating that many patients relapse and die despite available therapies [8, 9]. In addition, adjuvant chemotherapy is associated with adverse events that negatively impact patients' quality of life (QoL) [10]. Due to the unmet need for treatments which improve the outcomes of patients with NSCLC, novel targeted therapies and immunotherapies are currently under investigation in clinical trials and have been evaluated by health technology assessment (HTA) agencies [11–13].

Despite ongoing advancements in therapeutic approaches, the treatment of NSCLC is associated with high direct and indirect costs for patients, caregivers and healthcare services due to factors that appear to increase them (cost drivers) such as the progressive nature of the disease and associated mortality [14–17]. Costs are multifactorial but are attributable to components such as hospitalisation, surgery, chemotherapy, radiotherapy, productivity losses and travel for both patients and caregivers (where applicable) [10, 18, 19]. NSCLC therefore places an economic burden on society as a whole[14–17]. A robust understanding of costs and resource use of NSCLC is therefore a vital component for informing decisions regarding access to new therapies made by HTA agencies and reimbursement authorities.

The objective of this systematic literature review (SLR) was to provide a comprehensive overview of the available direct medical costs, direct non-medical costs, indirect costs, cost drivers and resource use data available for patients with early-stage NSCLC. It uses an exploratory approach; given that issues inherent with the comparison of evidence across studies due to their heterogeneity (which includes methodological variation, differences in sample groups , costing approaches, currency, country, treatments evaluated and follow-up periods) have influenced the estimated costs reported.

2 Methods

2.1 Study Design

An SLR was conducted to identify published cost and resource use data associated with patients with early-stage NSCLC (resectable, stage I–III) receiving treatment in the adjuvant or neoadjuvant setting. The searches were performed in March 2021 and updated in June 2022, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20].

2.2 Data Sources and Search Strategy

The following databases were searched on 18 March, 2021 via the Ovid platform: Embase; MEDLINE (including Epub ahead of print, in-process and other non-indexed citations and daily update); Evidence-Based Medicine Reviews (incorporating the Cochrane Database of Systematic Reviews, American College of Physicians [ACP] Journal Club, Database of Abstracts of Reviews of Effects [DARE], Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Methodology Register, HTA database and the National Health Service Economic Evaluation Database [NHS EED]); and EconLit. The search was updated on 22 June, 2022. The full search strategy (Online Resource 1 in the electronic supplementary material [ESM]) included free-text words, subject index headings (e.g. medical subject headings [MeSH]) and Boolean terms in order to capture studies which report costs and resource use for early-stage NSCLC. Additional searches of conference proceedings, reference lists of included publications, HTA bodies and additional sources and websites were conducted (Online Resource 2, ESM) using free-text terms.

2.3 Eligibility Criteria

Eligibility criteria for the SLR were defined by the PICO (population, interventions, comparators and outcomes) framework and study design, described in Table 1. There were no restrictions in terms of study country; however, there were some primary territories of interest and restrictions on publication date. These territories of interest and

restrictions were relevant to the scope of this review which was conducted as part of a broader body of work. Reference lists of review publications were checked using PICO criteria to ensure any relevant primary studies were considered for inclusion. Full publications reporting cost and resource use were selected for further analysis. Additionally, it was anticipated that a large volume of relevant studies would be identified in the SLR; therefore, the following additional criteria were prioritised for full data extraction and are the focus of this manuscript: full publications; data reported for countries of primary interest; sample size > 200 patients to reduce the potential impact that limitations with small studies can have on the results (e.g. selection bias).

2.4 Study Selection and Data Extraction

Screening was completed by two independent analysts at title/abstract stage (LJ/PH) and at the full publication stage (LJ/PH). Any disputes were referred to a third analyst (SB) and resolved by consensus.

Data extraction was conducted by a single analyst and 100% of data elements were checked by a second analyst. Disputes were referred to a third analyst and resolved by consensus. The extracted parameters included study characteristics (e.g. study design, country, and currency and reference year), sample details (e.g. sample summary, sample size, study period, inclusion and exclusion criteria), cost collection approach and cost valuation method, cost results (direct, indirect, cost drivers and resource use), methods/results of regression analyses and a summary of the study-reported conclusions and limitations.

2.5 Quality and Relevance Assessment

During data extraction, quality assessment of the included cost and resource use studies was undertaken using the checklist adapted to cost of illness by Molinier et al. [21].

3 Results

3.1 Search Yield

The electronic database search conducted in March 2021 identified a total of 3071 citations (Fig. 1). After the removal of duplicates, 2706 titles and abstracts were screened, of which 195 citations were deemed potentially relevant. Following full paper review, a further 96 publications were excluded, and grey literature searches yielded an additional three publications. In total, this search identified 40 full publications in countries of primary interest with a sample size > 200 reporting on cost and resource use for

Table 1 Eligibility criteria

Criteria	Include	Exclude
Population	Patients with early-stage NSCLC (resectable; stage 0/I/II/III) receiving treatment in the adjuvant or neoadjuvant treatment settings—no restriction with regard to patient age or mutation status[a]	Advanced/metastatic (stage IV) NSCLC Mixed populations where a breakdown of data for early-stage NSCLC is not provided
Intervention and comparators	No restriction	
Outcomes	Direct costs: Medical (e.g. medications, staff, hospitalisations, management of AEs) Non-medical (e.g. travel, childcare) Indirect costs Cost drivers Healthcare resource use	Non-cost and/or resource use related outcomes
Study design	Studies reporting original cost/resource use data	Reviews/editorials[b] Case reports Pharmacokinetic studies Animal/*in vitro* studies
Geography	No restriction; however, the following countries were of primary interest: Australia, Brazil, Canada, China, France, Germany, Italy, Japan, South Korea, Spain, UK and the US	
Publication date	2011 onwards (last 10 years)	Pre-2011
Language	No restriction; English language publications or non-English language publications with an English abstract were of primary interest	

AE adverse event, *NSCLC* non-small cell lung cancer, *UK* United Kingdom, *US* United States

[a]The primary population of interest was patients with stage II–III resectable disease; however, studies considering patients with stage I–III disease were considered eligible during the screening process to assess the extent of evidence available.

[b]The reference lists of any relevant review publications were checked to ensure any relevant primary studies were considered for inclusion

the sample of interest. An additional 29 conference abstracts and 33 publications reporting on countries that were not of primary interest and/or with a sample size of < 200 were also identified. The updated search conducted in June 2022 yielded two additional full publications and one conference abstract reporting on cost and resource use. The 30 conference abstracts and 33 publications from countries that were not of primary interest and/or sample size < 200(citation details in Online Resource 3 and Online Resource 4, respectively, see ESM) are not considered further in this SLR. Thefinal list of included publications that met the eligibility criteria for inclusion in the SLR and additional criteria for data extractionconsisted of 42 full publications.

3.2 Description of Identified Studies

A summary of the characteristics of included studies is provided in Table 2 with full details and extracted results provided in Online Resource 5 (see ESM). The articles were published between 2011 and 2021 and included data from 11 countries (Belgium, Canada, China, France, Germany, Italy, South Korea, Spain, The Netherlands, UK and the US)[1]. Two studies were multi-national; one study considered France, Germany and the UK and one study considered Belgium, the Netherlands and the UK. All other included studies reported cost or resource use in a single country. No data were found specifically for Australia, Brazil, or Japan, which were also countries of primary interest. A total of 28 studies included

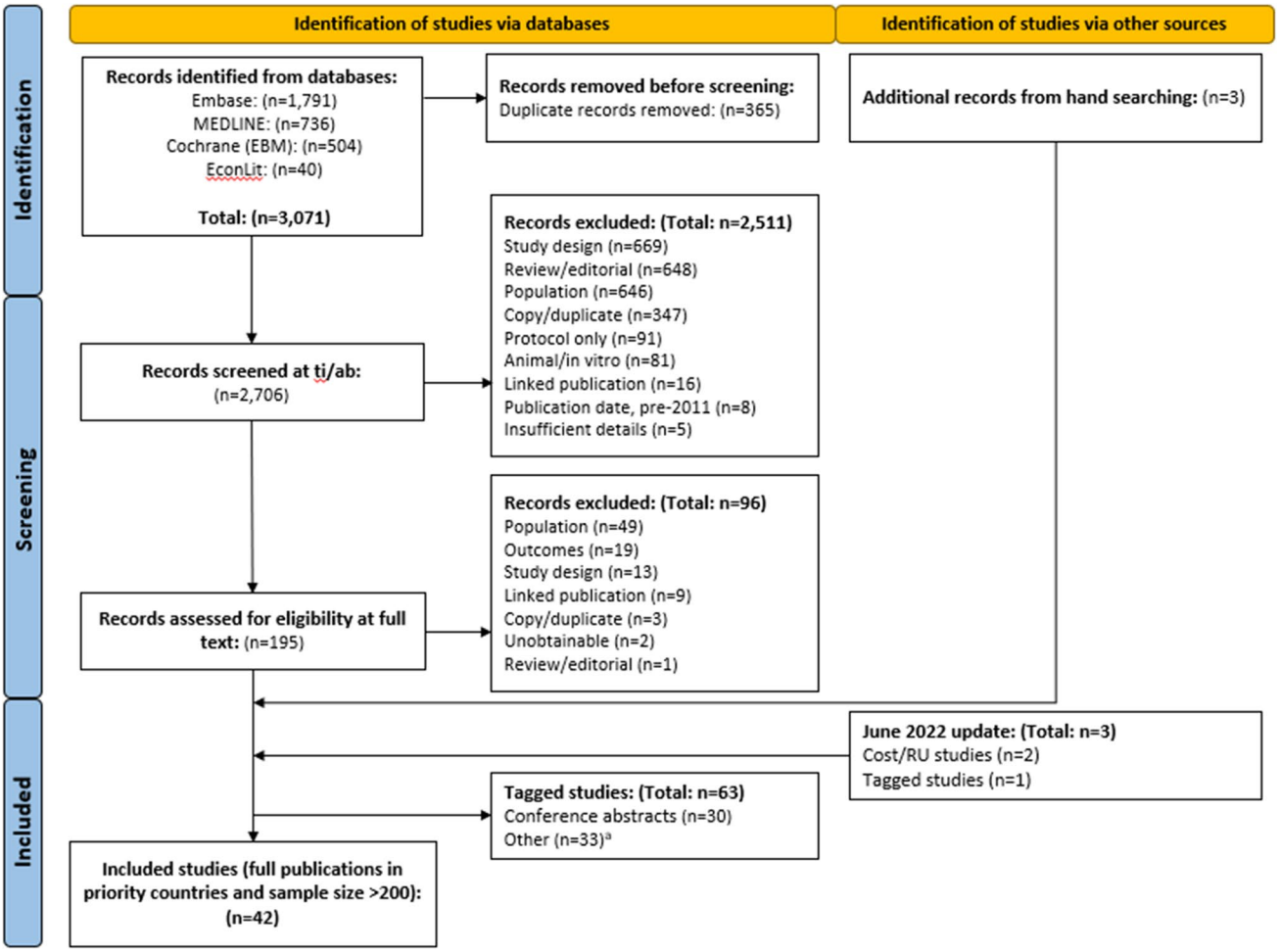

Fig. 1 PRISMA flow diagram of study selection for the cost and resource use SLR. [a]'Other' tagged studies are those which did not meet the additional criteria for full data extraction (i.e. conference abstracts and studies from countries which were not of primary interest and/or sample size < 200). EBM, evidence based medicine; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RU, resource use; SLR, systematic literature review; ti/ab, title and abstract

[1] Note that multi-national studies which included countries of primary interest also included additional countries.

Table 2 Summary characteristics of included studies

Study, country	Study design[a]	Follow-up period	Currency (year)	Costing approach	Disease stage (sample size)	Treatment line (if applicable)	Reported	
							Direct medical costs	Resource use
Abdellateef et al., 2020 [58] China	Prospective cohort	13–56 months	RMB (NR)	Bottom up	Stage IA NSCLC ($N = 491$)	First-line, surgery	✓	✓
Andreas et al., 2018 [15] France, Germany, UK	Cost analysis	Median: 26 months	EUR (2013)	Bottom up	Stage IB–IIIA NSCLC ($N = 306$)	NA	✓[b–d]	✓
Bouabdallah et al., 2020 [61] France	Propensity-matched cohort	12 months	EUR (NR)	Bottom up	Primary NSCLC ($N = 13,027$)	First-line, surgery	✓	✓
Buck et al., 2015 [22] US	Retrospective study	Varied by patient	USD (2013)	Bottom up	Stage IB to IIIA NSCLC ($N = 609$)	First-line, surgery	✓	✓
Buja et al., 2021 [14] Italy	Cost analysis	12 months	EUR (2019)	Bottom up	Stage I/II/III/IV/Pan-coast NSCLC (NR)	NA	✓	X
Cai et al., 2021 [23] US	Retrospective study	Median: 31.7 months	NA (resource use only)	NA	Stage II–IIIB NSCLC ($N = 456$)	Adjuvant	X	✓
Corral et al., 2015 [50] Spain	Cost analysis	3 years	EUR (2008)	Bottom up	Lung cancer ($N = 232$)	NA	✓[d]	X
Cowper et al., 2020 [51] US	Cost analysis	4 years	USD (2018)	Bottom up	Stage I–IV NSCLC ($N = 18,456$)	First-line, surgery	✓[d]	✓
Erb et al., 2016 [24] US	Retrospective study	2 years	NA	NA	Stage I NSCLC ($N = 9321$)	Supportive care	X	✓
Farrow et al., 2020 [25] US	Retrospective study	Unclear	NA (resource use only)	NA	pT1–3 N1–2 M0 NSCLC ($N = 13,462$)	NA	X	✓
Flanagan et al., 2015 [26] US	Retrospective study	Claims for PFT within 180 days of resection and for CT and PET within 90 days of resection	USD (NR)	Bottom up	Lung cancer ($N = 15,951$)	First-line, surgery	✓	✓
Geller et al., 2018 [27] US	Retrospective study	90 days	USD (NR)	Bottom up	NSCLC ($N = 488$)	First-line, surgery	✓	✓
Gildea et al., 2017 [28] US	Retrospective study	0.9–1.8 years	USD (NR)	Bottom up	Stage I–IV NSCLC ($N = 1210$)	NA	✓	✓
He et al., 2011 [29] China	Retrospective study	Unclear	USD (NR)	Bottom up	Stage I–IIIA NSCLC ($N = 1058$)	First-line, surgery	✓	✓
Hu et al., 2014 [30] US	Retrospective study	30 days	NA (resource use only)	NA	NSCLC ($N = 11,432$)	First-line, surgery	X	✓

Table 2 (continued)

Study, country	Study design[a]	Follow-up period	Currency (year)	Costing approach	Disease stage (sample size)	Treatment line (if applicable)	Reported	
							Direct medical costs	Resource use
Huang et al., 2018 [31] China	Retrospective study	Median: 27 months	CNY (NR)	Unclear	Stage I NSCLC ($N = 389$)	First-line, surgery	✓	✓
Hubert et al., 2018 [32] Canada	Retrospective study	Unclear	NA (resource use only)	NA	Early-stage (AJCC stage I or II) NSCLC ($N = 646$)	First-line, surgery	X	✓
Jean et al., 2019 [33] US	Retrospective study	90 days	USD (2011)	Bottom up	Stage I NSCLC ($N = 3530$)	First-line, surgery	✓	✓
Kennedy et al., 2016 [34] UK	Retrospective study	12 months	GBP (2013/2014)	Bottom up	Lung cancer ($N = 1883$)	NA	✓[d]	X
Lanuti et al., 2014 [35] US	Retrospective study	5 years	USD (NR)	Unclear	Stage I–IV NSCLC ($N = 1025$)	NA	✓[d]	✓
Lee, 2019 [36] South Korea	Retrospective study	Unclear	USD (NR)	Unclear	Stage I/II NSCLC ($N = 451$)	First-line, surgery	✓	✓
Li et al., 2019 [37] China	Retrospective study	Unclear	CNY (NR)	Unclear	Stage I NSCLC ($N = 1075$)	First-line, surgery	✓	✓
Louie et al., 2014 [54] Canada	Economic evaluation	10 years	CAD (2013)	Bottom up	Stage I NSCLC ($N = 25{,}085$)	Second-line, radiotherapy following surgery	✓	X
Mahar et al., 2014 [38] Canada	Retrospective cohort	4 years	USD (2012)	Bottom up	NSCLC ($N = 3354$)	First-line, surgery + adjuvant therapy	✓[d]	✓
Mei et al., 2019 [39] China	Retrospective study	> 5 years	RMB (NR)	Unclear	Stage I–II NSCLC ($N = 1485$)	First-line, surgery	✓	✓
Mittmann et al., 2020 [40] Canada	Retrospective study	12 months	CAD (NR)	Bottom up	Lung cancer ($N = 34{,}809$)	NA	✓	X
Presley et al., 2017 [41] US	Retrospective study	12 months	NA (resource use only)	NA	Stage I NSCLC ($N = 7955$)	First-line, surgery/radiotherapy	X	✓
Puri et al., 2015 [44] US	Retrospective study	30 days	NA (resource use only)	NA	Stage I–III NSCLC ($N = 129{,}893$)	First-line, surgery	X	✓
Radkani et al., 2016 [42] US	Retrospective study	Median: 249.41 days	NA (resource use only)	NA	Stage I–IIIA NSCLC	First-line, surgery	X	✓

Table 2 (continued)

Study, country	Study design[a]	Follow-up period	Currency (year)	Costing approach	Disease stage (sample size)	Treatment line (if applicable)	Reported	
							Direct medical costs	Resource use
Ramos et al., 2012 [52] France	Cost analysis	30 days	EUR (NR)	Bottom up	Stage I or II NSCLC ($N = 287$)	First-line, surgery	✓	✓
Rintoul et al., 2014 [55] UK, Belgium, Netherlands	Economic evaluation	Time horizon: 6 months	EUR (2010)	Bottom up	Confirmed or suspected potentially resectable NSCLC requiring mediastinal staging based on CT and PET-CT ($N = 241$)	Supportive care	✓[d]	✓
Rosen et al., 2017 [43] US	Retrospective study	2 years	NA (resource use only)	NA	Invasive NSCLC ($N = 59{,}734$)	First-line, surgery	X	✓
Sancheti et al., 2018 [53] US	Cost analysis	Unclear	USD (NR)	Bottom up	Stage I lung cancer ($N = 490$)	First-line, surgery	✓	✓
Shah et al., 2018 [49] US	Retrospective study	Varied by patient	USD (NR)	Bottom up	Stage I–IV NSCLC with or without COPD ($N = 66{,}963$)	NA	✓[d]	✓
Singnurkar et al., 2020 [45] Canada	Retrospective study	3 years	CAD (2017)	Unclear	Stage I/II NSCLC ($N = 6890$)	NA	✓	X
Smith et al., 2015 [56] US	Economic evaluation	5 years	USD (2014)	Bottom up	Early localised (<5 cm) NSCLC ($N = 1086$)	First-line, surgery	✓	X
Stone et al., 2021 [57] Canada	Economic evaluation	Unclear	CAD (2019)	Bottom up	Patients with a new lung cancer diagnosis[e] ($N = 350$: NSCLC, $N = 260$; SCLC, $N = 45$; Presumed lung cancer, $N = 45$)	First line, surgery, radiation therapy or thoracic surgery	X[b–d]	✓
Veluswamy et al., 2020 [46] US	Retrospective study	Unclear	USD (2012)	Bottom up	Stage I–IIIA NSCLC ($N = 2766$)	First-line, surgery	✓	✓
Vernon et al., 2016 [47] Canada	Retrospective study	19 months	CAD (2012)	Bottom up	Primary NSCLC ($N = 315$)	First-line, surgery	✓	✓

Table 2 (continued)

Study, country	Study design[a]	Follow-up period	Currency (year)	Costing approach	Disease stage (sample size)	Treatment line (if applicable)	Reported	
							Direct medical costs	Resource use
Voong et al., 2019 [48] US	Retrospective study	90 days	USD (2014)	Bottom up	Stage II–III NSCLC ($N = 297$)	NA	✓	✓
Yang et al., 2015 [59] China	Prospective cohort	12 months	USD (NR)	Bottom up	NSCLC ($N = 300$)	First-line, surgery	✓[d]	✓
Zhang et al., 2020 [60] China	Prospective cohort	Unclear	USD (NR)	Bottom up	Early-stage NSCLC ($N = 774$)	First-line, surgery	✓[e]	✓

AJCC American Joint Committee on Cancer, *CAD* Canadian dollar, *CNY* Chinese yuan, *COPD* chronic obstructive pulmonary disease, *CT* computed tomography, *EUR* euro, *GBP* Great Britain pound, *NA* not applicable, *NR* not reported, *NSCLC* non-small cell lung cancer, *PET* positron emission tomography, *PFT* pulmonary function test, *RMB* renminbi, *SCLC* small cell lung cancer, *UK* United Kingdom, *US* United States, *USD* US dollar

[a]Study design recorded as reported in the publications; therefore, some study designs may be similar but use different names

[b]Other outcomes reported by this study include direct non-medical costs

[c]Other outcomes reported by this study include indirect costs

[d]Other outcomes reported by this study include cost drivers

[e]74.3% of patients collected prospectively had NSCLC and 12.9% of patients had SCLC. As the majority of patients had NSCLC, this publication was eligible for inclusion

in the SLR were retrospective analyses [22–49], six were cost analyses (studies which measured cost and/or resource use outcomes only) [14, 15, 50–53], four were economic evaluations (comparative analyses of the costs and health outcomes of two alternative interventions) [54–57], three had a prospective cohort design [58–60] and one propensity-matched cohort study [61] was also included. Study sample sizes ranged from 232 to 129,893 and studies reported costs or resource use for samples covering multiple or individual stages of NSCLC and different treatment regimens.

3.3 Quality Assessment

Quality assessment of the 42 studies revealed that objectives were generally well defined across studies and results were presented consistently with the methodologies adopted (Online Resource 6, see ESM). However, few studies could conduct sensitivity analyses of model input variables ($n = 5$) [14, 54–57] and only three of these studies conducted sensitivity analyses to test the robustness of major assumptions [14, 57, 61]. One retrospective study incorporated a sensitivity analysis to determine the impact of varying unit costs on the total costs [38]. Additionally, it was often unclear if costs were appropriately discounted.

Commonly reported limitations acknowledged across the studies included inherent limitations of retrospective study designs (selection bias and unidentifiable confounders) ($n = 13$) [25, 29, 37, 39, 42, 43, 45, 47, 48, 53, 56, 60, 62]; restricted generalisability of results beyond the study setting to real-world practice ($n = 14$) [14, 23, 24, 26, 28, 30, 32, 33, 37, 39, 41, 47, 51, 53]; inherent limitations of claims data/databases used in analyses (e.g. missing information, miscoding) ($n = 11$) [22–25, 28, 41, 43–45, 49, 61]; limited follow-up periods ($n = 6$) [22, 28, 37, 40, 51, 60]; relatively small sample sizes ($n = 5$) [15, 45, 55, 56, 62]; and the failure to consider indirect costs ($n = 4$) [14, 34, 40, 52].

3.4 Direct Medical Costs

A total of 32 studies reported direct medical costs associated with patients with early-stage NSCLC [14, 15, 22, 26–29, 31, 33–35, 37–40, 45–56, 58–62].

3.5 Direct Medical Cost Data by Disease Stage

Eight studies reported direct medical cost data by disease stage (Table 3 and Online Resource 5, see ESM) [14, 22, 28, 40, 49–51, 54]. In general, costs were observed to increase with increasing pathological stage of disease, with patients with advanced disease incurring higher costs than those with early-stage disease [14, 28, 40, 49–51]. In early-stage disease, surgery was the primary driver of cost, whereas in the more advanced stages, radiotherapy,

medical therapy, treatment for progression and supportive care became increasingly important [14, 50]. For example, in one Spanish study, the mean (standard deviation [SD]) cost per patient over the 3 years following diagnosis or until death was €13,321 (€8316) for patients with stage I NSCLC and €15,044 (€14,338) for patients with stage IV NSCLC [50]. Surgery was the primary driver of this cost in stage I patients (58.9%), decreasing to 45.9% and 15.0% in stage II and stage III patients, respectively [50]. In patients with stage III disease, inpatient care (27.1%) and chemotherapy (20.8%) were the primary cost drivers [50]. Similarly, in an Italian study by Buja et al. (2021) [14], the mean (95% confidence interval [CI]) total direct costs per patient during the first year after diagnosis increased from €16,291 (15,284–17,505) in patients with stage I disease to €22,175 (22,127–22,190) in patients with stage IV disease. As the SLR did not include studies that focussed only on patients with advanced NSCLC, the exact conclusion may have differed if they were also included. However, such studies were not included in the review as its main focus is on patients with early-stage NSCLC. Moreover, a comparison of the healthcare resource use and cost of early-stage versus advanced-stage NSCLC patients seems most appropriate when taken from studies that focus on both groups of patients. It is plausible to assume that for studies that only focus on one group of patients, differences in aspects such as data and methodology would limit the possibility of making a comparison.

3.6 Intervention-Specific Direct Medical Cost Data

A total of 14 studies reported costs for different treatment options (surgical approaches and/or radiotherapy) for patients with early-stage NSCLC (Table 4 and Online Resource 5, see ESM) [29, 37–39, 46, 50, 52–54, 56, 58–61]. The costs of a range of surgical approaches were reported. In studies reporting costs for surgery, chemotherapy and radiotherapy, surgery was the most expensive treatment in patients with stage I and II NSCLC [38, 50, 54]. Four studies considered the comparison of video-assisted thoracoscopic surgery (VATS) versus open surgery (thoracotomy or sublobar resection) [39, 46, 56, 61]. In general, VATS was associated with lower costs than open thoracotomy [39, 46, 56]. Veluswamy et al. (2020) [46] also compared VATS with robot-assisted surgery (RAS) in patients with stage I–IIIA NSCLC identified from the US-based Surveillance, Epidemiology and End Results (SEER)-Medicare database; RAS-treated patients incurred significantly higher total costs (US$54,702 vs US$48,729; $p = 0.02$) and preoperative costs (US$3668 vs US$2803; $p < 0.0001$) compared with VATS-treated patients. However, costs were similar between the two minimally invasive procedures during the operative (US$28,732 vs US$27,209; $p = 0.078$) and post-operative (US$22,302 vs US$18,718; $p = 0.15$) periods [46]. Few studies reported costs associated with adjuvant therapy; however, where reported this was also an important driver of costs across all early stages of disease. One study reported few differences in regimen or healthcare resource use by disease stage associated with adjuvant treatment of patients with stage IB to IIIA NSCLC treated in community oncology practices in the US; the total monthly median cost per patient during adjuvant treatment was US$17,389.75 (interquartile range [IQR]: 8815.61–23,360.85) whereas the monthly cost from diagnosis until the end of the initial systemic therapy regimen after recurrence or the end of medical record was US$1185.08 (IQR: 250.60–2535.99) [22]. In a multi-national study assessing the economic burden of resected stage IB–IIIA NSCLC, the largest monthly direct costs per patient in the UK were for the adjuvant treatment period (€2490, based on 98 patients); whereas in France and Germany, monthly direct costs per patient were highest during the distant metastasis/terminal illness phase followed by the adjuvant phase [15].

3.7 Direct Non-medical Costs

Only two studies were identified that reported direct non-medical costs, one of which was in patients with early-stage NSCLC [15] and the other was in patients with newly diagnosed lung cancer, the majority of whom were patients with early-stage NSCLC [57].

Andreas et al. [15] estimated the burden and cost of illness associated with completely resected stage IB–IIIA NSCLC in France, Germany and the UK. Out-of-pocket (OOP) expenses were estimated based on the patient survey 3-month recall period and included childcare costs and transportation costs. The mean (95% CI) total OOP expenses per patient were €0 in France, €126 (100–158) in Germany and €132 (120–145) in the UK. The lack of OOP expenses in France was due to the high coverage of these costs by the national health insurance. These OOP costs may represent the total direct non-medical costs.

Stone et al. [57] reported that implementation of a multidisciplinary cancer clinic (MDC) model led to a reduction in patient visits and direct patient and caregiver costs compared with a traditional model of care for patients with lung cancer in Canada. Data were extracted for 78 patients with lung cancer (69 had NSCLC) from the traditional model and 350 patients (260 had NSCLC) from the MDC model. Total OOP savings for all patients studied in the MDC model compared with the traditional model was Can$24,167, or Can$69 per patient. This was attributed to Can$2226 in parking costs and Can$21,941 in return travel costs.

Table 3 Direct medical cost data by disease stage in patients with NSCLC

Study Country Currency (year)[a]	Direct medical cost data				
	Stage I	Stage II	Stage III	Stage IV	Stage unknown/ other
Buja et al., 2021 [14] Italy EUR (2019)	**Mean total direct costs per patient during the first year after diagnosis (95% CI):**				
	€16,291 (15,284–17,505)	€19,530 (18,263–21,091)	€21,938 (20,271–25,252)	€22,175 (22,127–22,190)	€21,328 (−20,897 to 22,322)
Buck et al., 2015 [22] US USD (2013)	**Median total cost of care PPPM by disease stage (IQR) during adjuvant treatment:**				
	Stage IB ($N = 63$): $17,495.64 (12,258.13–23,291.50)	Stage IIA/II ($N = 52$): $19,178.60 (6798.71–22,463.90) Stage IIB ($N = 48$): $17,784.05 (8152.45–24,341.09)	Stage IIIA ($N = 65$): $13,659.36 (9807.96–23,735.01)		Overall ($N = 228$): $17,389.75 (8815.61–23,360.85)
	Median total cost of care PPPM by disease stage (IQR) from diagnosis to end of first regimen after disease recurrence or end of medical record:				
	Stage IB ($N = 158$): $495.22 (128.43–1570.08)	Stage IIA/II ($N = 81$): $1368.32 (248.16–2210.36) Stage IIB ($N = 67$): $1713.95 (719.10–2964.43)	Stage IIIA ($N = 101$): $1578.55 (734.18–3837.78)		Overall ($N = 407$): $1185.08 (250.60–2535.99)
Corral et al., 2015 [50] Spain EUR (2008)	**Aggregate total costs:**				
	€519,526	€177,320	€475,846	€1,068,133	€307,835
	Mean total cost per patient with NSCLC over the 3 years following diagnosis or up to death (SD):				
	€13,321 (€8316)	€16,120 (€7632)	€13,218 (€10,240)	€15,044 (€14,338)	€20,522 (€19,336)
Gildea et al., 2017 [28] US USD (NR)	**Mean total healthcare costs, PPPM (SD) prior to diagnosis:**				
	$2667 ($3421)	$2456 ($2790)	Stage IIIA: $2121 ($2359) Stage IIIB: $2503 ($4016)	$2298 ($3209)	All NSCLC: $2407 ($3364)
	Mean total healthcare costs, PPPM (SD) post diagnosis:				
	$7239 ($7611)	$9484 ($8520)	Stage IIIA: $11,193 ($8826) Stage IIIB: $17,415 ($53,839)	$21,441 ($29,777)	All NSCLC: $16,577 ($33,550)
Louie et al., 2014 [54] Canada CAD (2013)	**Mean lifetime cost per patient:**				
	$23,115	$33,279	$30,156	$22,364	
Mittmann et al., 2020 [40] Canada CAD (NR)	**Mean medication costs per patient (95% CI):**				
	$612 (546–679)	$1415 (1278–1552)	$2291 (2155–2428)	$4207 (4060–4354)	$2900 (2816–2984)
	Mean radiation treatment costs per patient (95% CI):				
	$7982 (7610–8353)	$13,002 (12,321–13,682)	$17,790 (17,416–18,165)	$8019 (7877–8160)	$8009 (7093–8925)

CAD Canadian dollar, *CI* confidence interval, *EUR* Euro, *IQR* interquartile range, *NR* not reported, *NSCLC* non-small cell lung cancer, *PPPM* per patient per month, *SD* standard deviation, *US* United States, *USD* US dollar

[a]Two studies that reported direct medical cost data did not report values for total costs [49, 51]; itemised direct medical cost data by disease stage are presented in Online Resource 5 (see ESM)

3.8 Indirect Costs

Two studies were identified that reported indirect cost data associated with patients with early-stage NSCLC [15, 60] and one study was identified that reported indirect cost data associated with patients newly diagnosed with lung cancer (the majority of which had NSCLC) [57].

Andreas et al. [15] estimated the costs associated with loss of productive time (changes in job status and lost workdays) and OOP expenses for patients with completely resected stage IB–IIIA NSCLC in France, Germany and the UK. Mean total indirect costs (95% CI) per patient were estimated to be €696 (292–1172) for France, €2476 (1716–3289) for Germany and €1414 (620–2336) for the

Table 4 Direct medical cost data by intervention

Study Country Currency (year)[a]	Surgery	Chemotherapy	Radiotherapy
Abdellateef et al., 2020 [58] China RMB (NR)	**Median total cost per patient (range):** Intercostal: RMB 45,277 (35,967.69–66,711.48) Subxiphoid: RMB 51,535 (34,535–61,100)	NR	NR
Bouabdallah et al., 2020 [61] France EUR (NR)	**Mean cost per patient (SD):** Index stay: VATS: €9474.3 (€7225.7) Open thoracotomy: €10,417.6 (€6580.4) At 12 months: VATS: €14,247.1 (€12,614.7) Open thoracotomy: €16,869.8 (€14,903.7)	NR	NR
Corral et al., 2015 [50] Spain EUR (2008)	**Mean cost per patient with NSCLC over study period [SD]:** Stage I: €7849 [€4515] Stage II: €7401 [€4898] Stage III: €1989 [€4159] Stage IV: €322 [€1610] Stage unknown: €6574 [€6133]	Stage I: €699 [€2179] Stage II: €2511 [€4887] Stage III: €2749 [€6452] Stage IV: €6876 [€13,283] Stage unknown: €7402 [€18,928]	Stage I: €327 [€745] Stage II: €594 [€811] Stage III: €721 [€978] Stage IV: €327 [€661] Stage unknown: €60 [€232]
He et al., 2011 [29] China USD (NR)	**Mean total costs per patient by surgical approach (SD):** Complete VATS: $5155.7 ($655.4) Assisted VATS: $2617.2 ($35.3)	NR	NR
Li et al., 2019 [37] China CNY (NR)	**Mean total cost per patient:** Unmatched cohorts: Robotic: ¥93,321.45 (¥13,612.65) VATS: ¥66,926.81 (¥14,895.24) Matched cohorts: Robotic: ¥93,244.84 (¥13,799.48) VATS: ¥67,055.82 (¥11,877.03)	NR	NR
Louie et al., 2014 [54] Canada CAD (2013)	**Initial direct costs per case for stage I NSCLC:** Sublobar resection: $12,161.17 Lobectomy: $16,266.12 Pneumonectomy: $22,940.59	NR	$7646.98
Mahar et al., 2014 [38] Canada USD (2012)	**Mean cost per patient (SD):** Pneumonectomy: $12,004.76 (–) Lobectomy: $11,914.89 (–) Segmentectomy: $11,952.51 (–)	$2374.90 ($1741)	$6522.31 (–)
Mei et al., 2019 [39] China RMB (NR)	**Mean total hospital cost per patient, (SD):** All enrolled patients: VATS ($N = 737$): ¥48.1 (¥11.1) Open thoracotomy ($N = 748$): ¥36.5 (¥17.4) After propensity score matching: VATS ($N = 464$): ¥48.4 (¥11.3) Open thoracotomy ($N = 464$): ¥35.5 (¥9.4)	NR	NR
Ramos et al., 2012 [52] France EUR (NR)	**Mean total costs per patient stratified by surgical approach (SD):** Thoracoscopy: €11,934.13 (€6690.25) Thoracotomy: €14,145.57 (€7117.84)	NR	NR

Table 4 (continued)

Study Country Currency (year)[a]	Surgery	Chemotherapy	Radiotherapy
Smith et al., 2015 [56] US USD (2014)	**Mean weighted costs through 5 years of follow up:** (a) SABR versus sublobar resection: SABR: $55,120 Sublobar resection: $77,964 (b) SABR versus lobectomy: SABR: $54,968 Lobectomy: $82,641	NR	NR
Sancheti et al., 2018 [53] US USD (NR)	**Median hospital costs per patient (IQR):** Surgical approach: Thoracoscopy ($N = 375$): $16,439.35 Thoracotomy ($N = 72$): $24,294.81	NR	NR
Veluswamy et al., 2020 [46] US USD (2012)	**Mean total costs per patient:** RAS: $54,702 VATS: $48,729	NR	NR
Yang et al., 2015 [59] China USD (NR)	**Total cost per patient over 12-month study period:** 3D VATS: $11,486.73 2D VATS: Total: $11,388.21	NR	NR
Zhang et al., 2020 [60] China USD (NR)	**Mean direct costs (SD):** Before propensity score matching: Robotic ($N = 298$): $7631.10 ($1642.10) VATS ($N = 476$): $7512.20 ($1400.30) After propensity score matching: Robotic ($N = 257$): $7719.00 ($1668.50) VATS ($N = 257$): $7496.40 ($1285.60)	NR	NR

CNY Chinese yen, *EUR* euro, *IQR* interquartile range, *NR* not reported, *NSCLC* non-small cell lung cancer, *RAS* robot-assisted surgery, *RMB* renminbi, *SABR* stereotactic ablative body radiotherapy, *SD* standard deviation, *US* United States, *USD* US dollar, *VATS* video-assisted thoracoscopic surgery

[a]Itemised costs and costs for whole patient cohorts, patient subgroups, or treatment type, where reported, are presented in Online Resource 5 (see ESM)

UK. In the study by Zhang et al. [60], the mean indirect costs associated with robotic thoracic surgery and VATS in patients with early-stage NSCLC were compared. Indirect costs included hospital overhead cost and amortisation of capital equipment, including of the purchase and maintenance of minimally invasive platforms. The results revealed a higher mean indirect cost in the robotic group ($n = 298$) compared with the VATS group ($n = 476$; US$4300.20 [SD US$23.00] vs US$338.30 [SD US$19.80]; $p < 0.01$).

Stone et al. [57] calculated the change in patient and caregiver productivity to derive the total productivity gains of an MDC treatment model for patients with lung cancer in Canada compared with a traditional model. The study also calculated the time forgone for return travel, parking and finding the clinic, as well as clinic visit costs, calculated from administrative personnel hourly wages. Due to 371 fewer visits to MDC than the traditional model clinic, total productivity gains of Can$23,714 (Can$6379 for patients and Can$17,335 for caregivers) were reported. In addition, due to the reduction in visits associated with the MDC model, net administrative savings for the time spent booking clinic visit appointments of Can$508 (Can$1.37 per visit) were estimated.

3.9 Resource Use

A total of 16 studies reported resource use data associated with patients with early-stage NSCLC (Online Resource 5, see ESM) [15, 22–24, 26, 28, 35, 38, 41, 46–49, 51, 55, 57]. Five studies reported resource utilisation by patients with

different stages of disease [22, 28, 35, 49, 51]. Resource use was not found to differ significantly by stage in studies that considered only patients with early-stage disease [22]; however, there were differences in resource use between patients with early and advanced (stage IV) disease stages (28, 49, 51]. For instance, Cowper et al. [51] found that brain imaging was used more often to stage patients with advanced disease (46% for stages II–IV vs 30% for stage I) and invasive mediastinal staging was less common in pathological stage I patients than in those with more advanced disease (28.9% vs 41–50%). Similarly, Gildea et al. [28] reported that per patient per month healthcare utilisation after lung cancer diagnosis was significantly higher among patients diagnosed at stage IV disease and lowest among patients diagnosed at stage I disease. Both studies were US-based [28, 51].

The choice of treatment approach also had an impact on healthcare resource utilisation rates [27, 29, 37–39, 41, 46, 59, 60]. For instance, Veluswamy et al. [46] reported lower rates of positron emission tomography scans, chest computed tomography scans and mediastinoscopy in patients undergoing RAS compared with both VATS and open thoracotomy. In addition, geographical region was demonstrated to influence resource utilisation regardless of treatment approach. For example, Mahar et al. [38] conducted a population-based retrospective cohort study of patients with resected NSCLC in Canada and reported that rates of chemotherapy usage, the proportion of patients who received any imaging scans, hospitalisations, specialist visits, emergency room visits, mean number of imaging scans, General Practitioner visits and blood transfusions all varied significantly among Canadian geographic regions over a 4-year follow up period.

4 Discussion

The objective of this SLR was to provide a comprehensive overview of the available direct medical costs, direct non-medical costs, indirect costs, cost drivers and resource use data available for patients with early-stage NSCLC.

The majority of studies reported direct medical cost data. In general, direct medical costs were observed to increase with increasing pathological stage of disease [14, 15, 22, 26–29, 31, 33–35, 37–40, 45–56, 58–62]. Cost drivers varied according to disease stage, with surgery being the predominant contributor to costs in the early stages of disease, and radiotherapy, medical therapy, treatment for progression and supportive care becoming increasingly important with more advanced disease [14, 50]. Treatment approach was also found to influence direct medical costs, with minimally invasive surgery options generally incurring less costs than more traditional open surgical approaches [39, 46, 56]. Robotic surgical systems have also been shown to be safe and effective in resectable NSCLC and could make up for the deficiencies of traditional thoracoscopic surgery; however, the relatively expensive cost has become a major factor in limiting their widespread use [31]. Overall, the evidence collated highlights the costs and healthcare requirements associated with early-stage NSCLC and is in line with a recent review of the economic burden of lung cancer (all histological subtypes), which also demonstrated the considerable economic burden that lung cancer imposes on patients and healthcare systems [17].

The strengths of this SLR include the design of the search strategy and the wide range of data sources searched. Only full publications were analysed as the limited reporting in conference abstracts implies a lack of robustness as a data source in comparison with full publications. Despite the identification of a reasonable number of studies ($n = 42$), the ability to compare results was limited due to study heterogeneity. Methodological variations between the included studies as well as differences in sample groups (cancer types and stages), costing approaches, currency, country, treatments evaluated and follow-up periods influenced the estimated costs reported. Findings from this review must also be interpreted with consideration of the individual study caveats and limitations of the overarching evidence base. Prospective studies with extended follow-up periods would help to reduce bias (e.g. due to sample selection, missing information) and ensure that long-term information relating to costs and resource utilisation are appropriately captured in this sample.

The current review has highlighted a number of data gaps in the published literature. Firstly, there is a paucity of robust evidence relating to the indirect costs and direct non-medical costs associated with patients with early-stage NSCLC in the primary countries of interest. This limits the ability to make comparisons of the economic impact of different treatments. Future studies should seek to build on the current evidence base by calculating a comprehensive cost of illness of early-stage NSCLC, including both direct and indirect costs, to fully elucidate the burden of this disease. There is also a clear need for more studies comparing the apparent advantages of RAS with the increased cost of technology [42, 46]. The current evidence base is heavily US-centric (20/42 studies) and patients from other markets will need to be included in future studies to address international and regional variations in costs and resource utilisation. This will assist with wider generalisability, ensuring that analyses that may rely on this data (e.g. economic evaluations) are appropriate to the territory of interest given differences in healthcare resource use and the cost of healthcare resources across markets. As treatment burden was found to vary markedly across patients and treatment types, future work should identify opportunities to further understand and ameliorate this

burden [41], such as studies evaluating the value of MDC models outside of Canada.

5 Conclusion

This study summarises the costs and healthcare resource use associated with early-stage NSCLC. Moreover, certain studies that were identified demonstrate that the economic burden of NSCLC may increase with disease progression [14, 28, 40, 49–51]. Preventing disease progression for patients with early-stage NSCLC therefore has the potential to reduce the economic burden of NSCLC on patients, caregivers and healthcare systems. Despite the data gaps identified, this review provides a comprehensive overview of the available cost and resource use data in this indication, which is fundamental for helping to understand the economic impact of NSCLC [14, 50].

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Declarations

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Author contributions NJ, SB, DDM and RB assisted with the SLR design, data analysis and manuscript preparation. PH designed the SLR and collected and analysed the data. SB collected and analysed the data. LGJ collected and analysed the data and assisted with manuscript preparation. All authors read and approved the final version of the manuscript.

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