Real-World Data on Metastatic Lung Cancer: Cost Analyses in Brazil From a Private Insurance Company's Perspective

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ABSTRACT

PURPOSE Non–small cell lung cancer (NSCLC) is often diagnosed at late stages, leading to escalated treatment expenses. This study aimed to elucidate the costs of lung cancer treatment in a private health care setting in Brazil.

MATERIALS AND METHODS We conducted a retrospective cohort study, regarding costs, survival, and quality of care of stage IV NSCLC in a private health company in Brazil.

RESULTS A total of 819 individuals were included, with median age 64.9 years. With a 1-year follow-up, patients had a median of four hospital admissions, with a median length of stay in of 6.2 days. Survival rates were higher for patients treated with targeted therapy (hazard ratio [HR], 0.38 [95% CI, 0.25 to 0.56]), immunotherapy (HR, 0.52 [95% CI, 0.40 to 0.68]), or both treatments sequentially (0.41 [95% CI, 0.25 to 0.68]). Patients submitted to sequentially targeted therapy and immunotherapy had the higher total costs (mean, $172,828 USD) compared with patients treated with immunotherapy (mean, $138,125 USD), targeted therapy (mean, $117,068 USD), and only chemotherapy (mean, $47,625 USD). As expected, longer survival was translated into more third-line therapy ($P < .001$), and higher mean costs with cancer-related hospital admissions ($24,554 USD chemo, $31,835 USD immuno, $28,228 USD targeted, and $35,494 USD for both therapies). However, costs did not increase in proportion to the survival benefit. Despite longer survival, patients undergoing targeted therapy or immunotherapy had median number of hospital admissions and length of stay similar to those who underwent chemotherapy alone.

CONCLUSION Higher survival rates and costs were found for patients exposed to modern treatments for advanced NSCLC. Cost-effectiveness thresholds definitions are warranted for managing costs, particularly in developing countries.

ACCOMPANYING CONTENT

Data Supplement

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INTRODUCTION

Non–small cell lung cancer (NSCLC) is the second most common cancer type worldwide, and the leading cause of cancer mortality.[1] In Brazil, NSCLC tends to be diagnosed late, with a 2-month delay from initial oncology consultation to treatment.[2] Advances such as immunotherapy (immune checkpoint inhibitors) and targeted therapy have improved patients outcomes but increased costs, straining health care budgets because of extended treatment durations, toxicities, and costly technologies.[3-7]

The challenge of lung cancer care in Brazil worsens with limited funding, resource disparities, and the need for strategic planning and understanding of treatment costs.[2,9] Despite screening programs, advanced-stage diagnoses are more common among lower socioeconomic groups, leading to higher metastatic disease rates and lower survival.[8] Public-private health care disparities such as limited access to invasive biopsy delay diagnosis.[2] Only *EGFR*, *ALK*, and PD-L1 tests are covered by insurance, while most patients access next-generation sequencing (NGS) through a pharmaceutical-funded program. Scarce data on private care real-world treatment costs highlight the need for improved resource allocation.[10,11]

This study aims to review the real-world costs of patients with stage IV NSCLC covered by private insurance, treated in different institutions in Brazil. This cost analysis will provide a source of information for future cost-effectiveness and budget-impact studies. Costs not covered by health insurance were excluded.

CONTEXT

Key Objective
What is the impact of metastatic lung cancer treatments in real-life costs and survival in private practice in Brazil?

Knowledge Generated
Targeted therapy in metastatic non–small cell lung cancer had a 62% survival advantage, with an increase in the mean total cost by 2.45. Immunotherapy had a survival advantage of 48%, with an increase in the mean total cost by 2.9 times. Sequentially targeted immunotherapy led to the highest total cost, with no survival benefit. Modern treatments did not increase the median number of hospital admissions or the length of stay.

Relevance
The assess of real-world costs of the lung cancer treatment and its relation to survival in private care in Brazil can provide a useful source of information for future studies of cost-effectiveness and budget impact of different therapeutic innovations for health insurance companies in Brazil.

MATERIALS AND METHODS

Study Setting and Design

We retrospectively analyzed patients from a multicentric national database of patients covered by a private insurance in Brazil and treated for metastatic NSCLC, candidates for systemic treatment between January 2016 and March 2021. Data were collected through treatment request reports of the health insurance database, and information systems that enable inventory control, input, and output, and administered drugs were also analyzed. This study was approved by the institutional review board and local ethics committee.

Study Procedures

Patients with the following characteristics were eligible for analysis: (1) patients with stage IV NSCLC; (2) received any systemic treatment; (3) covered by private health insurance throughout the study period; and (4) possibility of accessing treatment costs (available from the insurance database). All patients had lung cancer confirmed through biopsy. Data were collected from the treatment request reports of the health insurance database. Patients were evaluated and treated individually in their own institutions. Treatment indication was decided by the assisting oncologist. Patients were selected according to the treatment request form, and all patients included were screened through International Classification of Diseases 10th revision under malignant neoplasm of bronchus and lung (C34). Patients who lost their private insurance were excluded from our analysis. Patients who did not meet the inclusion criteria or were lost from follow-up were excluded. Patients who were candidates for systemic treatments approved by the Brazilian supplementary health regulatory agency (ANVISA) and with mandatory coverage by health insurance were included.

The following procedures were considered for analysis: direct medical costs, including chemotherapy, ambulatory visits, administration of infusion protocols, total costs of outpatient high-complexity tests such as magnetic resonance, computed tomography, positron emission tomography (PET) scintigraphy, total expenditure on low-complexity outpatient tests including laboratory tests and X-rays, total expenditure on outpatient procedures and therapies (physiotherapy, minor noninpatient procedures), emergency department visits, and hospital admissions.

Study Outcomes

The primary objective was to assess whether the incorporation of new drugs over the years has increased costs, survival, and the quality of care (direct costs).

Covariables' Definitions

Explanatory variables were divided into age, sex, city, and state of residence, number of treatment lines, median duration of patient coverage under the insurance, and median follow-up. We also analysed the percentage of patients who underwent at least one PET scan before treatment and after treatment initiation, number of hospital admissions, hospitalization days, and length of hospital stay.

Patients were followed-up until last medical information or death. Costs were converted from Brazilian Real into US dollars on June 2023 exchange rate (R$ 4.8 = $1 USD).

Lung cancer–related factors were evaluated, including type of systemic treatment, drug cost, number of systemic therapies received, and overall survival (OS). The treatments included in the immunotherapy group were pembrolizumab, atezolizumab, and nivolumab. Targeted therapy treatments include afatinib, alectinib, crizotinib, erlotinib, gefitinib, larotrectinib, nintedanib, and osimertinib. The remaining

treatments for other driver mutations were not found in our database. Patients treated with monoclonal antibodies such as bevacizumab and ramucirumab, in the absence of treatment with immunotherapy or targeted therapy, were included in the chemotherapy group, but a cost analysis of these drugs was carried out separately (Data Supplement). Patients were staged according to the seventh edition of the TNM lung cancer staging system. OS was defined as the duration from the date of diagnosis until death. The costs were aggregated per patient, and thus, the sum of costs per year was calculated. All patients were analyzed according to each center protocol and treatment.

Statistical Analysis

Continuous variables were described using medians and quartiles. Categorical variables were described using absolute or relative frequencies. Comparison of baseline variables and costs according to therapies was performed using Kruskall-Wallis for continuous variables, and chi-square for categorical variables.

Overall and cancer-specific survival curves were constructed using the Kaplan-Meier method and compared using log-rank tests. Multivariate analysis of prognostic effect of covariates age, sex and days of admission on overall and cancer-specific survival was performed using Cox proportional hazard analysis and the effects of therapies were assessed using hazard ratios (HRs) along with their respective 95% CIs and *P* values.

The impact of therapies on hospitalization durations and hospital admissions was evaluated using a generalized linear model with a gamma family distribution and a log-link function.

Data analysis was conducted using R software version 4.1.2 (R software, Viena, Austria).

RESULTS

Patients Characteristics and Procedures

A total of 819 patients met the inclusion criteria and were candidates for systemic treatment (Fig 1). Median follow-up time was 1 year (IQR, 0.03-6 years). Median age was 64.9 years (IQR, 57.7-71.9), and 50% of the participants were of the female gender. The time covered by the health insurance plan was a median of 8.9 years (IQR, 4.3-16.4), not reflecting lung cancer follow-up, as it includes a period before the lung cancer diagnosis. They had a median of four hospital admissions in the period (IQR, 2-6) with a median length of stay in of 6.2 days (IQR, 3.8-10). Patients baseline characteristics including demographics are found in Table 1. Most patients were treated in two Brazilian states, Rio de Janeiro and São Paulo, comprising 35% and 44% of the total population, respectively (Data Supplement, Table S1).

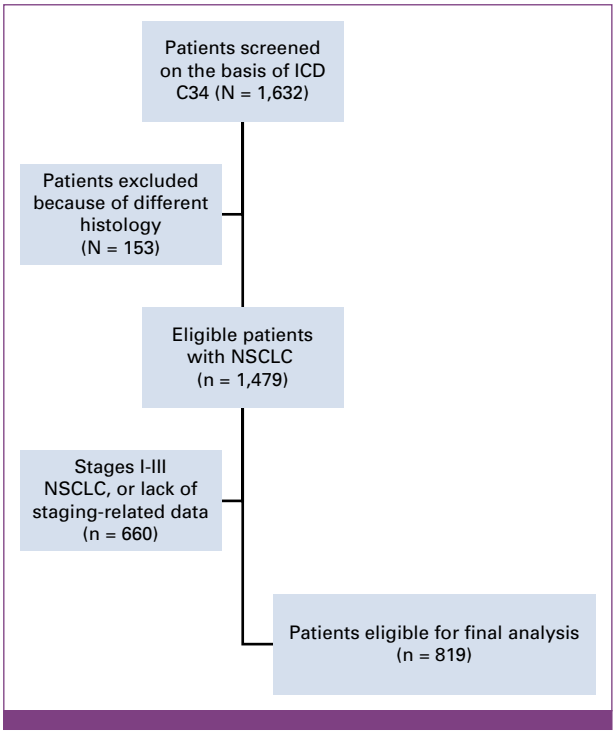

FIG 1. Flow diagram of patient enrollment and analysis. ICD, International Classification of Diseases; NSCLC, non–small cell lung cancer.

Molecular tests were funded by heath care insurance in 6% of patients treated with chemotherapy (12/201 patients), 5.9% of immunotherapy group (24/409), 5.6% of targeted therapy (8/144), and 9.2% of patients treated with immunotherapy and targeted therapy (6/65) (Data Supplement, Table S2). We did not have PD-L1 data as its insurance coverage started just in 2020, and they were performed by a pharmaceutical-sponsored program.

Throughout the period from 2016 to 2021, there was an increase in the total prescription of systemic therapies for advanced NSCLC in private health care in Brazil. Immunotherapy has been increasingly used, from 6.9% to 36%, while

TABLE 1. Clinical and Demographical Characteristics of Participants With Stage IV Non–Small Cell Lung Cancer From 2016 to 2021

Variable	N = 819
Median age, years (25%, 75%)	64.9 (57.7, 71.9)
Sex, n/N (%)	
Female	408/819 (49.8)
Male	411/819 (50.2)
No. of treatment lines, median (25%, 75%)	2 (1, 2)
Time (years) covered by insurance, median (25%, 75%)	8.9 (4.3, 16.4)
Hospital admissions, median (25%, 75%)	4 (2, 6)
Lengh of stay, median (25%, 75%)	6.2 (3.8, 10)

chemotherapy use decreased from 72.3% to 37.3%. Chemotherapy is yet the most common treatment prescribed (53.1%) considering all periods (Fig 2 and Data Supplement, Fig S1). In recent years, targeted therapies approved in Brazil have been increasing, with a modest enhanced use (13.4%) (Fig 2 and Data Supplement, Table S2).

According to type of systemic treatment, 201 (24.5%) patients received only conventional chemotherapy, 409 (49.9%) received immunotherapy, 144 (17.5%) received targeted therapy (with or without chemotherapy), and 65 (7.9%) received both immunotherapy and targeted therapy sequentially as part of treatment (Table 2). Compared with participants receiving only chemotherapy, patients with targeted therapy were younger (62 years [IQR, 52.3-69.6] *v* 66.8 years [59.2-73.4], $P < .001$), and predominantly female (62% *v* 47%). Patients who received both targeted therapy and immunotherapy had more third-line treatments (34% *v* 3%), more hospital admissions (6 [IQR, 4-8] *v* 4 [2-6], $P < .001$), more PET scans performed after treatment (71% *v* 34%), and a higher number of total of PET scans (3 [1-7] *v* 1 [0-2]) (Table 2).

Survival

Patients receiving targeted therapy or immunotherapy showed superior OS compared with those on chemotherapy alone (Fig 3). After Cox regression adjustment for age, sex, and the number of hospitalization days, the benefits on OS of targeted therapy (HR, 0.38 [95% CI, 0.25 to 0.56]) or immunotherapy (HR, 0.52 [95% CI, 0.40 to 0.68]) became more evident. However, combining both therapies in treatment sequencing did not significantly affect OS, despite the greater number of therapies performed. Age slightly increased mortality, and each additional 10 hospital days raised mortality risk by 3% (Table 3).

The estimated 1-year OS was 74.5% in the total cohort. According to subgroups, the 1-year OS was 54.3%, 77.1%, 87.7%, and 86.7% in chemotherapy, immunotherapy, targeted therapy, and immunotherapy + targeted therapy groups, respectively.

In multivariate analysis adjusted for age, compared with the group that received only chemotherapy, despite an increase in survival, the addition of immunotherapy or targeted therapy to systemic treatment did not significantly increase the length of hospital stay (HR, 1.06; $P = .522$, and HR, 1.03; $P = .829$, respectively). However, patients on sequential targeted therapy and immunotherapy had longer hospital stays compared with the chemotherapy alone group (HR, 1.44; $P = .015$) (Data Supplement, Table S4). Also, in age-adjusted multivariate analysis, the addition of immunotherapy and/or targeted therapy did not increased the number of hospital admissions (Data Supplement, Table S5).

Costs

The overall costs for stage IV NSCLC treatments increased significantly from 2016 to 2021, rising from $3.3 million USD in 2016 to $15.6 million USD in 2020 (Data Supplement, Fig S2). Mean per-patient therapy costs also rose from $12,000 USD (median, $8,100 USD [IQR, 3,000-17,000]) in 2016 to $26,800 USD (median, $12,100 USD [IQR, 3,200-37,600]) in

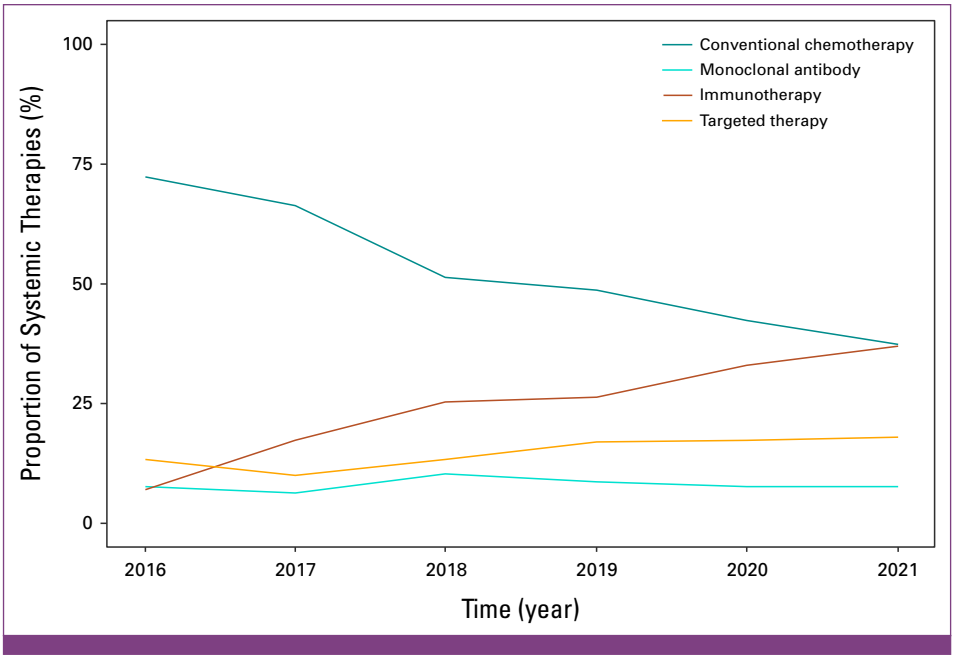

FIG 2. Proportion of systemic therapies administered for participants with stage IV non–small cell lung cancer between 2016 and 2021.

TABLE 2. Characteristics of Participants According to Systemic Treatments for Stage IV Non–Small Cell Lung Cancer

Variable	Chemotherapy (n = 201)	Immunotherapy (n = 409)	Targeted Therapy (n = 144)	Immunotherapy + Targeted Therapy (n = 65)	*P*
Age, years, median (25%, 75%)	66.8 (59.2, 73.4)	65.4 (59.3, 71.7)	62 (52.3, 69.6)	62.6 (51.9, 71.2)	<.001
Sex: Female, n/N (%)	94/201 (47)	184/409 (45)	89/144 (62)	41/65 (63)	<.001
Treatment lines, median (25%, 75%)	1 (1, 2)	2 (1, 2)	2 (1, 2)	2 (2, 3)	<.001
At least one treatment of first line, n/N (%)	185/201 (92)	387/409 (95)	135/144 (94)	61/65 (94)	.673
At least one treatment of second line, n/N (%)	33/201 (16)	157/409 (38)	40/144 (28)	38/65 (58)	<.001
At least one treatment of third line, n/N (%)	6/201 (3)	66/409 (16)	14/144 (9.7)	22/65 (34)	<.001
Insurance covering time, median (25%, 75%)	8.4 (3.6, 13.9)	9.1 (4.6, 18.4)	8.4 (3.9, 14.6)	10.2 (5.9, 14.9)	.075
At least one PET scan before treatment, n/N (%)	84/201 (42)	230/409 (56)	72/144 (50)	38/65 (58)	.006
At least one PET scan after treatment, n/N (%)	69/201 (34)	244/409 (60)	100/144 (69)	46/65 (71)	<.001
Total of PET scans, median (25%, 75%)	1 (0, 2)	2 (1, 3)	2 (1, 4)	3 (1, 7)	<.001
Hospital admissions, median (25%, 75%)	4 (2, 6)	4 (2, 7)	4 (2, 6)	6 (4, 8)	<.001
Length of stay, median (25%, 75%)	6.5 (4, 10.7)	6 (3.9, 9.5)	5.8 (3.4, 10.4)	7.3 (3.9, 9.8)	.540

Abbreviation: PET, positron emission tomography.

2020 (Data Supplement, Fig S3 and Table S3). Costs were highest for patients receiving immunotherapy plus targeted therapy, averaging $172,828 USD (median, $147,885 USD [IQR, 87,537-252,523]) compared with $47,625 USD (median, $38,188 USD [IQR, 20,259-62,994]) for chemotherapy alone. Longer survival increased total drug costs (mean, $128,383 USD and median, $99,001 USD [IQR, 48,523-181,078] *v* mean, $19,223 USD and median, $8,088 USD [IQR, 3,168-20,736]), emergency department visits (mean, $912 USD and median, $338 USD [IQR, 240-823] *v* mean, $432 USD and median, $281 USD [IQR, 131-536]), high-complexity examinations (mean, $6,206 USD and median, $6,006 USD [IQR, 2,461-8,877] *v* mean, $2,358 USD and median, $1,652 USD [IQR, 949-2,871]), low-complexity examinations (mean, $1,251 USD and median, $820 USD [IQR, 523-1,662] *v* mean, $895 USD and median, $371 USD [IQR, 207-677]), and outpatient procedures and therapies (mean, $2,289 USD and median, $838 USD [IQR, 325-2,174] *v* mean, $895 USD and median, $286 USD [IQR, 53-843]).

Molecular tests, primarily NGS, were typically funded by the pharmaceutical consortium, as only *EGFR* and *ALK* tests are covered by insurance. *EGFR*/*ALK* test costs were mean $958.6 USD (standard deviation [SD], 200.1) and median $1,037.6 USD (983.5-1,037.6) in the chemotherapy group, mean $982.8 USD (SD, 212.8) and median $983.5 USD (953.9-1,037.6) in the immunotherapy group, mean $996.4 USD (SD, 20) and median $983.5 USD (983.5-1,008) in the targeted therapy group, and mean $1,009.7 USD (SD, 47.1) and median $1,037.6 USD (983.5-1,037.6) in patients treated

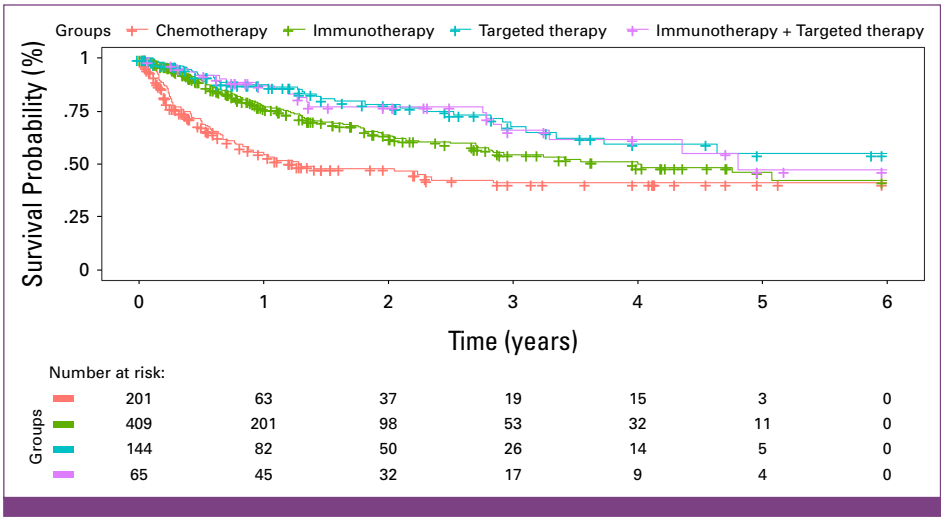

FIG 3. Kaplan-Meier survival curves displaying survival time in years by treatment subtype for patients diagnosed with stage IV non–small cell lung cancer.

TABLE 3. Multivariate Cox Regression Analysis of Factors Associated With Time to Death (all-cause) in Patients Diagnosed With Stage IV, Non–Small Cell Lung Cancer

Variable	HR	95% CI	*P*
Age, years	1.02	1.01 to 1.03	<.001
Sex			
Female	—	—	
Male	1.21	0.95 to 1.54	.114
Days of hospitalization/10	1.03	1.01 to 1.05	.002
Treatment			
Conventional chemotherapy	—	—	
Immunotherapy	0.52	0.40 to 0.68	<.001
Targeted therapy	0.38	0.25 to 0.56	<.001
Immunoterapy + targeted therapy	0.41	0.25 to 0.68	<.001

Abbreviation: HR, hazard ratio.

with immunotherapy and targeted therapy (Data Supplement, Table S6).

We analyzed separately the costs of first- and second-line immunotherapy treatment, and also according to the mechanism of action (anti–PD-1 *v* anti–PD-L1). Costs have increased over the years, but there was no significant difference between drugs. Since we assessed total costs in a retrospective nature analysis, it is expected that patients treated in second line or more would have higher costs than those treated in the first line (Data Supplement, Tables S7 and S8).

Patients submitted to sequentially targeted therapy and immunotherapy had the higher total costs compared with the group treated with immunotherapy ± chemo (mean, $138,125 USD and median, $99,375 USD [IQR, 65,260-187,957]) and targeted therapy ± chemo (mean, $117,068 USD and median, $79,694 USD [IQR, 35,336-168,403]). Total hospitalization costs were significantly higher in patients with targeted therapy and/or immunotherapy. Despite survival gain exceeding 50%, the hospitalization cost did not increase proportionally (Table 4).

DISCUSSION

This study examines factors influencing systemic treatment cost in patients with stage IV NSCLC in a private health insurance in Brazil from 2016 to 2021. Immunotherapy use rose from 6.9% to 37% after Brazilian regulatory approval of nivolumab for previously treated stage IV lung cancer (April 2016), and pembrolizumab in first-line treatment in December 2018. However, our population is behind the optimal use of immunotherapy.[12-14] Patients receiving immunotherapy and targeted therapy not only had the highest survival probability, but also the highest costs, driven by emergency department visits, examinations, outpatient procedures and therapies, and hospital admissions specifically for participants under immunotherapy plus targeted therapy. Conversely, the survival benefit of patients receiving targeted therapy was similar, regardless of the use of immunotherapy, what reinforces the low level of evidence of immunotherapy prescription in patients with driver mutations, including regard costs.

Molecular profiling costs reflect only *EGFR* and *ALK* tests funded by insurance, representing <10% of tests, as most NGS were funded by a pharmaceutical consortium (Data Supplement, Table S2).

Since chemotherapy offers limited survival and quality-of-life benefits in metastatic lung cancer, the treatment and follow-up costs are crucial to consider balancing costs and benefits of medical interventions.[15] A few retrospective longitudinal studies[16,17] estimated the cost of metastatic lung cancer in the United States, but did not track lifetime health care resource use nor analyzed cost components by setting or service type. Up-to-date data on resource use and costs among patients with metastatic lung cancer including components may impact on the optimal allocation of health care resources.

We found a similar incidence of advanced NSCLC among sex (50%), probably because of the increasing number of women smokers in the past 30 years.[18]

We provided a picture of disease treatment costs, from the perspective of a private insurance company provider. Although most patients (53.1%) received chemotherapy, those treated with target therapy and/or immunotherapy had better OS ($P < .001$), in accordance to literature.[18-20]

Immunotherapy and targeted therapies incurred median total costs 2.9 and 2.4 times higher than chemotherapy, respectively, with survival benefits of 48% and 62%, highlighting a gap between costs and survival improvements, prompting discussions on oncology expenses and strategies to make treatments more affordable. Our analysis showed that patients treated with immunotherapy with or without chemotherapy received more lines of systemic treatment and presented better survival than those in chemotherapy ($P < .001$). Given the retrospective nature of data collection, we expected that patients with longer survival had greater exposure to systemic treatment.[21]

Preventing the effects of financial hardship from cancer is imperative, as one in two survivors report financial distress.[22] Cancer costs affect patients and families, leading to sacrifices to cover expenses and affecting treatment adherence, symptoms, quality of life, survival.[23,24]

Historically, hospitalizations have driven cancer costs; but, with costly therapies (such as immunotherapy and target therapy), prescription drugs and outpatient care may become significant cost drivers. Our data show the highest mean hospitalization cost for immunotherapy ($31,835 USD)

TABLE 4. Costs of Patients With Stage IV Lung Cancer From 2016 to 2021 in a Private Care Setting in Brazil

Costs 2016-2021	Chemotherapy (n = 602)	Immunotherapy (n = 581)	Targeted Therapy (n = 214)	Immunotherapy + Targeted Therapy (n = 82)	*P*
Total costs					<.001
Mean (SD)	47,625 (40,602)	138,125 (111,204)	117,068 (119,831)	172,828 (103,467)	
Median (25%, 75%)	38,188 (20,259, 62,994)	99,375 (65,260, 187,957)	79,694 (35,336, 168,403)	147,885 (87,537, 252,563)	
Drug costs <1 year after diagnosis					<.001
Mean (SD)	12,893 (15,804)	52,749 (43,049)	32,557 (30,987)	40,833 (32,258)	
Median (25%, 75%)	6,539 (2,813, 14,394)	41,080 (22,326, 73,433)	19,833 (10,556, 49,575)	30,543 (18,201, 53,229)	
Drug costs >1 year after diagnosis					<.001
Mean (SD)	6,329 (19,340)	47,173 (89,524)	47,092 (84,345)	87,550 (90,682)	
Median (25%, 75%)	0 (0, 363)	620 (0, 59,289)	7,043 (0, 56,094)	56,656 (10,792, 132,301)	
Total drug costs					<.001
Mean (SD)	19,223 (28,283)	99,922 (101,090)	79,649 (94,562)	128,383 (93,955)	
Median (25%, 75%)	8,088 (3,168, 20,736)	65,214 (34,314, 129,250)	47,283 (14,335, 105,983)	99,001 (48,523, 181,078)	
Total hospital admissions					.042
Mean (SD)	24,554 (29,997)	31,835 (43,376)	28,288 (43,497)	35,494 (42,857)	
Median (25%, 75%)	17,985 (6,909, 31,706)	21,146 (7,826, 37,238)	16,200 (5,653, 34,805)	20,820 (11,404, 44,035)	
Office visits					<.001
Mean (SD)	436 (362)	629 (473)	650 (593)	830 (679)	
Median (25%, 75%)	334 (197, 548)	518 (273, 867)	489 (266, 829)	678 (405, 1,086)	
Emergency visits					.063
Mean (SD)	432 (488)	518 (616)	574 (726)	912 (1,664)	
Median (25%, 75%)	281 (131, 536)	328 (153, 677)	360 (152, 736)	338 (240, 823)	
High-complexity examinations[a]					<.001
Mean (SD)	2,358 (2,256)	4,048 (4,061)	4,499 (4,523)	6,206 (4,326)	
Median (25%, 75%)	1,652 (949, 2,871)	3,140 (1,945, 5,027)	3,392 (1,874, 6,307)	6,006 (2,461, 8,877)	
Low-complexity examinations[b]					<.001
Mean (SD)	895 (4,680)	854 (740)	867 (1,010)	1,251 (1,209)	
Median (25%, 75%)	371 (207, 677)	663 (356, 1,069)	597 (331, 952)	820 (523, 1,662)	
Procedures[c]					<.001
Mean (SD)	895 (1,759)	2,009 (6,783)	4,378 (25,431)	2,289 (4,271)	
Median (25%, 75%)	286 (53, 843)	362 (102, 1,337)	322 (70, 1,147)	838 (325, 2,174)	

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SD, standard deviation.
[a]Total costs on highly complex outpatient examinations (MRI, CT, PET, scintigraphy, etc)—does not include expenses with chemotherapy.
[b]Total costs on low-complexity outpatient examinations (laboratory examinations, X-rays, etc).
[c]Total cost on outpatient procedures and therapies (physiotherapy, minor noninpatient procedures, etc).

and immunotherapy plus targeted therapy groups ($35,934 USD). Patients with longer survival are exposed to more interventions, increasing outpatients costs. In our population, the mean hospitalization costs did not increase in the same magnitude as drug costs, or the survival benefits. No significant differences were found in the admissions rates and length of stay between therapy groups, suggesting these treatments do not compromise care quality.

As cancer costs escalate, health insurance premiums increase risking patients's access to private health care. From 2013 to 2019, cancer treatment costs in Brazil has increased 40.5%, specially with new drug mandatory coverages.[25] In the United States, high deductible health plans are an affordable alternative, but retrospective analysis show association with lower overal and cancer-specific survival.[26]

Yabroff et al estimated a metastatic lung cancer last year of life's costs of care in $85,392 (in 2010 USD); hospitalization was the largest component of cost.[27] This estimate included patients with lung cancer who died of other causes, and did not include outpatient prescription medications. Similar to the reported costs by Lang et al, among patients receiving first-line doublet chemotherapy.[17] Vera-Llonch et al[28] estimate a mean health care cost of $125,849 USD, higher than those previous studies that lacked cost components, highlighting a gap our study aimed to address.

Caution should be exercised in generalizing our study's results to other patient populations and settings. We used a large Brazilian private health insurance database on resource utilization and costs of active employees, dependents, and insurance-eligible retirees.

Two additional studies reported costs of $40,226 (in 2010 USD) (excluding chemotherapy) and $12,584 USD, respectively, for the past 6 months of life among patients in a Veteran Affairs medical center and those in terminal phase, respectively.[28-30] Most studies did not track the full lifetime costs of metastatic lung cancer.

Longer survival is linked to better physical condition, increased use of chemotherapy or outpatient services and reduced hospitalization.

A limitation of our study is the lack of inflation adjustment for payment amounts, as general or medical price index may not suit for this patient subset; our estimates reflect experiences from 2016 to 2022. We also did not consider nonmedical direct costs, which may add to the financial burden for long-term patients, or those in terminal situations.

The results presented in this study reinforce the importance of modern systemic therapy for longer NSCLC survival and the implication of direct costs. Our data highlight the rational use of modern therapy, guided by cost-effectiveness data, addressing right population to better benefit. We foresee the urgent need to earlier diagnosis in lung cancer in Brazil, to reduce costs with systemic therapies-either chemotherapy or modern therapies.

In conclusion, data on real-world treatment costs for advanced lung cancer are almost inexistent from health insurance companies in Brazil. The increased survival rates achieved through modern treatments have correspondingly resulted in higher direct costs. Consequently, private health care systems will need efficient cost management strategies to ensure comprehensive treatment accessibility.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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