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ORIGINAL RESEARCH

Financial Toxicity for Pembrolizumab and Atezolizumab for Metastatic Non-Small Cell Lung Cancer: A Pooled Analysis of Cost-Effectiveness Analyses

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Background: Immune checkpoint inhibitors (ICIs) were promising medical treatments for advanced or metastatic non-small cell lung cancer (NSCLC), while the financial toxicity could not be neglected due to the high cost which might impair the prognosis and quality of life. Thus, we compared the cost-effectiveness analyses to identify the potential financial toxicity of metastatic NSCLC received ICIs.

Methods: A systematic literature search was performed for the published economic evaluation of ICIs in the Medline and Web of Science databases between January 2015 and September 2021. Only the studies conducting the cost-effectiveness analysis, including total cost, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER), were included in our research. We compared the economic outcomes between the immunotherapy group and chemotherapy group and stratified by the programmed death receptor-1 ligand (PD-L1) expression. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist would be employed to check the quality of included papers.

Results: A total of 25 studies and 30 cost-effectiveness analyses were included, in which 22 (73.3%) were on Pembrolizumab, eight (26.7%) on Atezolizumab, and 17 (56.7%) on the American payer perspective. In total, the ICER was lower than the willingness to pay (WTP) in 43% of the included analyses. The ICER of Pembrolizumab was lower than that of Atezolizumab (P = 0.049), and it was comparable between ICER and WTP either for Pembrolizumab (P = 0.533) or Atezolizumab (P = 0.056). The economic outcomes were all comparable as stratified by the PD-L1 expression.

Conclusion: Immunotherapy could bring financial toxicity, and financial toxicity assessment during clinical decision would weaken the potential impact in the whole course of immunotherapy.

Keywords: financial toxicity, immunotherapy, metastatic non-small cell lung cancer, clinical decision

Introduction

In recent decades, lung cancer is the most common carcinoma with high incidence and mortality throughout the world, and more than half of the patients were categorized as advanced diseases during the first diagnosis.[1] Immunotherapy developed swiftly, and immune checkpoint inhibitors (ICIs) were promising medical treatments for advanced or metastatic non-small cell lung cancer (NSCLC), especially for the diseases with positive expression of programmed

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death ligand-1 (PD-L1).[2,3] Tumor proportion score (TPS) is referred to the positivity of PD-L1 expression in tumor cells, and high TPS was associated with a favored prognosis for those who received immunotherapy.

However, the impact of financial burden might not be neglected due to the high cost of the novel therapies, and patients might not be able to afford to continue the previous treatments.[4,5] Immunotherapies represented by Atezolizumab and Pembrolizumab demonstrate excellent efficacy for patients with NSCLC, but their annual treatment costs are significantly higher compared to chemotherapy.[6] The high expense of cancer treatment could bring great financial pressure, or even bankruptcy to the patients and their families, mainly consisting of the objective economic burdens and subjective perceptions of the poverties. In this way, the concept of financial toxicity was proposed, and it was reported to impair the quality of life and result in increased mortality. The comprehensive score for financial toxicity (COST) was the only validated tool for the financial toxicity assessment, and a prospective investigation that complied with the COST tool identified the definite financial toxicity of pan-cancer treatment in Japan.[4,5,7] Patients with NSCLC are unfavored for immunotherapy due to its high cost, which might lead to impaired survival. In different countries, drug prices further exacerbate financial toxicity.[8] In China, the drug price negotiation program and the National Reimbursement Drug List (NRDL) initiated in 2018 and led by the government, is a critical policy aimed at reducing the financial burden of medical treatments for patients. Although some advanced drugs and therapies have been included in the NRDL, which has partially reduced medical costs and alleviated financial toxicity, the prices of certain original immune checkpoint inhibitors remain high. Therefore, we aim to explore the financial toxicity of immunotherapy for patients with NSCLC.

Cost-effectiveness analysis was employed to evaluate the association between the survival benefit from immunotherapy and concomitant financial toxicity. Quality-adjusted life years (QALYs) are comprehensive and quantified assessments of health outcomes, including quality of life (QOL), and incremental cost-effectiveness ratio (ICER) is referred to as the cost per QALY gained. Willingness-to-pay (WTP) is the maximum cost that patients are regarded to afford for the therapy, and the comparison of WTP and ICER would help to interpret the survival benefit in the view of economics for immunotherapy. Various countries would set the target WTP in various ways based on their health policies, and it is commonly set as 100,000 or 150,000 US dollars per QALY.[6] While the cost was generally regarded as cost-effective when the ICER was lower than three times the country's per-capita gross domestic product (GDP), as suggested by the World Health Organization's Choosing Interventions that are Cost-Effective project (WHO-CHOICE).[9]

Recently, several studies have proposed the clinical implications of financial toxicity for medical treatment with high expense, and we aimed to investigate the role of financial toxicity in NSCLC after Pembrolizumab or Atezolizumab. We systematically reviewed the previously published studies with cost-effectiveness analysis, and we would also reveal the heterogeneity of financial toxicity stratified by TPS for NSCLC. We hypothesized that financial toxicity could have an adverse impact on survival and might be a crucial indicator in clinical practice for those with NSCLC who received immunotherapy.

Methods

The investigators conducted a systematic literature search for the published economic evaluation of ICIs (Pembrolizumab and Atezolizumab) in the Medline, and Web of Science databases between January 2015 and September 2021. We developed a free-word search in the following terms, Atezolizumab OR Pembrolizumab, non-small cell lung cancer OR lung cancer, and financial toxicity OR cost-effectiveness. All reference lists from the included papers were carefully reviewed to identify relevant studies.

The following inclusion criteria were employed in the selection process: (1) assess the cost-effectiveness of Pembrolizumab or Atezolizumab monotherapy or combined therapies for metastatic NSCLC; (2) several critical economic evaluation parameters were included, including QALY and ICER; (3) the willingness to pay (WTP) was clarified or WTP was mentioned in the study; (4) the papers presented base-case results for economic evaluation. The study would be excluded when it met one of the following criteria: (1) the critical data involving economic evaluation were not available; (2) the paper was not an original article, including (conference) abstract, case report, and review; (3) the paper was not presented in English. Two individual investigators conducted the study selection (WH and JHW), and the discrepancy would be decided by the third investigator (JL).

After identifying the included papers, two investigators (WH and JHW) extracted the data from the involved studies independently, and the difference was assessed and decided by the third investigator (JL). The following items were

collected from the papers: the last name of the first author, year of publication, statistical model, cost perspective, treatment therapy, total cost, incremental cost, QALY, incremental QALY, ICER, and WTP. The cost perspective referred to the specific country or area where the authors presented the cost of therapy and conducted the analyses in their research. As for the economic evaluation of the cost, QALY, and ICER, we only extracted data and conducted analyses on the base-case results. All costs had been converted into US dollars to facilitate the comparison of economic outcomes, and the exchange rate of currency conversion was intended to be the average value of the opening price and closing price of the published year of the research. When the WTP was unavailable in the study, it would be estimated as three times the country's per-capita GDP as conformed to the WHO-CHOICE principle.

We could compare the economic outcomes between the experimental group (ICI monotherapy or combined therapies) and the control group (mainly chemotherapy), including the incremental cost, QALY, and ICER. Afterwards, we would also compare such outcomes in the homogenous treatment subgroup with regard to various PD-L1 expressions. TPS is a general stratification system to show the PD-L1 expression of tumor cells in NSCLC, which would be divided into high expression (>50%) and low expression (1–49%). Moreover, we would review the critical findings from the sensitivity analyses for ICER estimation in each study. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist would be employed to check the quality of cost-effectiveness analyses.[10] The CHEERS checklist would inspect seven main parts of the study (title, abstract, introduction, methods, results, discussion, and other relevant information).

The continuous variables were compared with Student's *t*-test, and the paired-samples *t*-test would also be employed between groups. A two-tailed *P*-value <0.05 was identified as statistically significant. All statistical analyses were conducted in SPSS (version 25.0, IBM, Armonk, NY, USA), GraphPad Prism (version 9.2.3, GraphPad Software, San Diego, CA), and R (version 4.2.0, R Foundation for Statistical Computing, Vienna, Austria) were employed to visualize the statistical findings.

Results

A total of 25 studies met the inclusion criteria, and 30 cost-effectiveness analysis records were included[11–39] (Figure 1). We reviewed the characteristics and economic evaluation index of Pembrolizumab and Atezolizumab among all included studies (Table 1) and described the economic evaluation of Pembrolizumab stratified by the PD-L1 expression (TPS ≥ 50% and 1–49%; Table 2). Among the 30 records, 22 (73.3%) were on Pembrolizumab, eight (26.7%) on Atezolizumab,

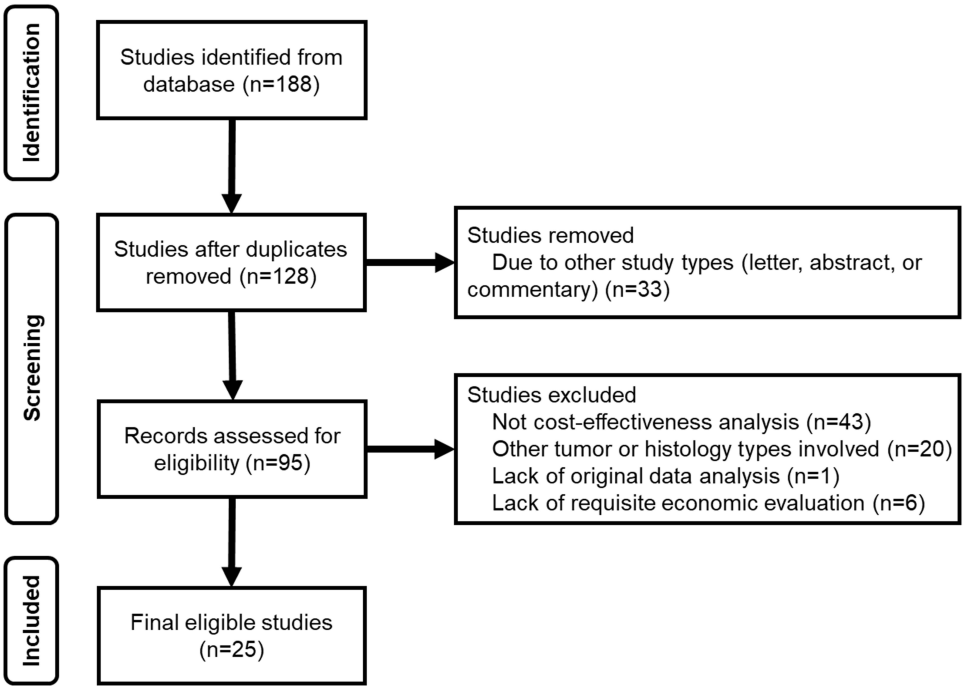

Figure 1 The PRISMA flowchart for study selection.

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Table 1 The Characteristics of the Included Studies and Economic Evaluation of Pembrolizumab and Atezolizumab Among the Included Total Trial Population

Article, Year	Data Resource	Statistical Model	Cost Perspective	Experimental Group			Control Group			ΔQALY[d] (Year)	ICER (Dollars/ Year)	WTP (Dollars)
				Treatment	QALY (Year)	ΔCost[a,b] (Dollars)	Treatment	QALY (Year)	Cost[c] (Dollars)			
Huang, 2016[27]	KEYNOTE-010	PSM	US	Pembro	1.71	160522	Chemo	0.76	136,921	0.95	168,619	200000
Huang, 2017[28]	KEYNOTE-024	PSM	US	Pembro	2.60	102439	Chemo	1.55	260,223	1.05	97,621	200000
Hu, 2018[25]	KEYNOTE-024	Markov	UK	Pembro	1.54	94929	Chemo	0.71	26,682	0.83	113,856	65500
Bhadhuri, 2019[23]	KEYNOTE-024	PSM	Switzerland	Pembro	3.05	78601	Chemo	1.71	149,189	1.34	58,550	102000
Loong, 2019[13]	KEYNOTE-024	PSM	China	Pembro	1.69	32380	Chemo	1.41	116,832	0.29	112,475	130490
Chouaid, 2019[e21]	KEYNOTE-024	PSM	France	Pembro	2.06	72020	Chemo	1.04	80,701	1.02	89,751	114013
Liao, 2019[22]	KEYNOTE-024	Markov	China	Pembro	1.10	46362	Chemo	0.65	68,657	0.45	103,128	26481
Aziz, 2020[12]	KEYNOTE-024	PSM	Singapore	Pembro	2.00	108988	Chemo	1.13	52,833	0.87	125,769	75000
Weng, 2020[f16]	KEYNOTE-042	Markov	US	Pembro	1.67	47030	Chemo	0.76	64,462	0.91	54,280	180000
Huang, 2019[18]	KEYNOTE-042	PSM	US	Pembro	1.77	63909	Chemo	1.28	167,046	0.49	130,155	194000
She, 2019[f20]	KEYNOTE-042	Markov	US	Pembro	1.95	77205	Chemo	1.46	172,835	0.49	158,795	150000
Zhou, 2019[24]	KEYNOTE-042	Markov	China	Pembro	2.42	53550	Chemo	1.04	30,000	1.37	39,403	26508
Insinga, 2018[26]	KEYNOTE-189	PSM	US	Pembro+Chemo	2.84	150888	Chemo	1.40	177,072	1.44	104,823	180000
Zeng, 2019[19]	KEYNOTE-189	Markov	US	Pembro+Chemo	1.61	151409	Chemo	0.83	137,123	0.78	194,372	171660
Wu, 2020[15]	KEYNOTE-189	Markov	US	Pembro+Chemo	2.57	142774	Chemo	1.40	198,863	1.17	122,248	150000
Wu, 2020[15]	KEYNOTE-189	Markov	China	Pembro+Chemo	2.42	52598	Chemo	1.30	52,327	1.11	47,328	29196
Wan, 2020[14]	KEYNOTE-189	Markov	US	Pembro+Chemo	1.66	102870	Chemo	0.88	153,551	0.78	132,392	100000
Wan, 2020[14]	KEYNOTE-189	Markov	China	Pembro+Chemo	1.37	54565	Chemo	0.78	61,072	0.59	92,533	27351
Insinga, 2021[11]	KEYNOTE-189	PSM	US	Pembro+Chemo	2.43	128575	Chemo	1.61	205,460	0.81	158,030	195000
Insinga, 2021[11]	KEYNOTE-407	PSM	US	Pembro+Chemo	2.30	86622	Chemo	1.81	160,641	0.49	178,387	195000
Wu, 2020[15]	KEYNOTE-407	Markov	US	Pembro+Chemo	2.39	124316	Chemo	1.36	159,481	1.02	121,375	150000
Wu, 2020[15]	KEYNOTE-407	Markov	China	Pembro+Chemo	2.16	44883	Chemo	1.34	41,084	0.82	54,805	29196
Liu, 2021[29]	IMpower110	Markov	China	Atezo	1.32	70347	Chemo	0.90	38,914	0.42	168,903	30828
Peng, 2021[30]	IMpower110	Markov	US	Atezo	2.36	224590	Chemo	1.08	86,464	1.32	170,730	150000
Ding, 2020[34]	IMpower130	Markov	US	Atezo+Chemo	1.68	109809	Chemo	1.52	259,003	0.16	670,310	150000
Lin, 2020[33]	IMpower130	Markov	US	Atezo+Chemo	0.99	105617	Chemo	0.67	102,345	0.32	333,199	180000
Criss, 2019[38]	IMpower150	Microsimu-lation	US	Atezo+Chemo+Beva	2.13	131615	Chemo +Beva	1.48	112,551	0.65	201,676	100000
Wan, 2019[37]	IMpower150	Markov	US	Atezo+Chemo+Beva	1.39	234998	Chemo +Beva	0.98	154,552	0.41	568,967	100000
Ondhia, 2019[35]	OAK trial	PSM	Canada	Atezo	1.31	62954	Chemo	0.71	33,663	0.60	105,135	92500
Marine, 2020[g32]	OAK trial	PSM	France	Atezo	1.27	57832	Chemo	0.80	19,099	0.47	122,657	135,574

Notes: ΔCOST[a], the higher cost of the experimental group (Pembrolizumab/Atezolizumab) above the control group (chemotherapy/chemotherapy+bevacizumab). ΔCOST[b], the exact cost listed in this table that was not recorded in US dollars had been converted to US dollars in accordance with the average exchange rate of the year when the study published (Hu 2018, 1 Great Britain Pound=1.31 US dollars; Bhadhuri 2019, 1 Schweizer Franken=1.02 US dollars; Loong 2019, 1 hong Kong dollar=0.13 US dollar; Chouaid 2019, 1 Euro=1.14 US dollars; Aziz 2020, 1 Singapore dollar=0.75 US dollar; Ondhia 2019, 1 Canadian dollar=0.74 US dollar; Marine 2020, 1 Euro=1.17 US dollars). COST[c], the exact total cost of the control group (chemotherapy/chemotherapy+bevacizumab). ΔQALY[d], the higher quality-adjusted life years brought from the experimental group (Pembrolizumab/Atezolizumab) above the control group (chemotherapy/chemotherapy+bevacizumab). Chouaid, 2019[e], the cost of the total trial population was not recorded in the published study, and the cost of the majority of the total trial population (patients with non-squamous cell carcinoma which range 75% of the entire study population) was regarded as the estimated cost of the total trial population. Weng, 2020[f], and She, 2019[f], the cost of the total trial population was not recorded in the published study, and in this way, the average cost of the subgrouped population (stratified by PD-L1 expression) was regarded as the estimated cost of the total trial population. Marine, 2020[g], the explicit willing to pay was not clarified in the study, and the estimated willingness to pay was set as three times of the local gross domestic product (France, 38625 euros) conformed to the and had been converted to US dollars in accordance with the average exchange rate in 2020.

Abbreviations: Atezo, atezolizumab; Beva, bevacizumab; Chemo, chemotherapy; ICER, incremental cost-effectiveness ratio; Pembro, pembrolizumab; PSM, partitioned-survival model; QALY, quality-adjusted life years; UK, the United Kingdom; US, the United States; WTP, willingness to pay.

Table 2 The Economic Evaluation of Pembrolizumab Stratified by the PD-L1 Expression (TPS ≥ 50% and 1–49%)

Article, Year	Data Resource	Cost Perspective	TPS ≥ 50%				TPS 1–49%			
			QALY (Year)	ΔQALY[a] (Year)	ΔCost[b] (Dollars)	ICER (Dollars/Year)	QALY (Year)	ΔQALY[a] (Year)	ΔCost[b] (Dollars)	ICER (Dollars/Year)
Weng, 2020[16]	KEYNOTE-042	US	1.87	1.13	53,784	47,596	1.37	0.59	39,827	68061
Huang, 2019[18]	KEYNOTE-042	US	2.05	0.77	NA	111781	1.56	0.28	NA	161546
She, 2019[20]	KEYNOTE-042	US	2.10	0.63	86,165	136,229	1.83	0.39	70,887	179530
Zhou, 2019[24]	KEYNOTE-042	China	2.81	1.79	65,322	36,493	2.16	1.12	44,133	39404
Insinga, 2018[26]	KEYNOTE-189	US	3.24	1.86	192,774	103,402	3.47	1.89	133,671	183529
Wu, 2020[15]	KEYNOTE-189	US	2.67	1.10	156,849	142,997	2.77	1.23	137,533	112088
Wu, 2020[15]	KEYNOTE-189	China	2.41	0.95	57,829	61,018	2.50	1.06	50,208	47400
Wan, 2020[14]	KEYNOTE-189	US	1.80	0.92	41,250	44,731	1.93	1.04	81,244	77754
Wan, 2020[14]	KEYNOTE-189	China	1.42	0.64	22,009	34,388	1.53	0.75	42,746	56768
Insinga, 2021[11]	KEYNOTE-189	US	2.74	0.73	125,144	171,332	2.36	0.64	121,113	189606
Insinga, 2021[11]	KEYNOTE-407	US	2.54	0.61	73,369	119,662	2.35	0.78	88,574	113999
Wu, 2020[15]	KEYNOTE-407	US	2.23	0.87	114,338	131,136	2.68	1.24	141,461	113780
Wu, 2020[15]	KEYNOTE-407	China	2.14	0.81	52,614	65,136	2.54	1.14	47,950	42,242

Notes: ΔQALY[a], the QALY brought from the experimental group (Pembrolizumab/Atezolizumab) above the control group (chemotherapy/ chemotherapy+bevacizumab) within each subgroup as stratified by PD-L1 expression. ΔCost[b], the higher cost of the experimental group (Pembrolizumab/Atezolizumab) above the control group (chemotherapy/chemotherapy+bevacizumab).

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not available; QALY, quality-adjusted life years; TPS, tumor proportion score; UK, the United Kingdom; US, the United States.

17 (56.7%) on the United States payer perspective, and 7 (23.3%) on the Chinese payer perspective. The median WTP of the total population, US population, and Chinese mainland population was 133,032 (range, 26,481–200,000) US dollars, 171,660 (range, 100,000–200,000) US dollars, and 28,274 (range, 26,481–30,828) US dollars, respectively.

As for the all included studies, the gained QALY (2.1 ± 0.5 years versus [vs] 1.6 ± 0.5 years, P = 0.024; Figure 2a) and incremental QALY (0.87 ± 0.31 vs 0.54 ± 0.35 years, P = 0.041; Figure 2b) of Pembrolizumab were superior to that of Atezolizumab (Table 3). The cost increment compared with the chemotherapy was comparable between Pembrolizumab and Atezolizumab (89883.4 ± 39644.8 dollars vs 124720.3 ± 69709.1 dollars, P = 0.215; Figure 2c), and the ICER of Pembrolizumab was lower than that of Atezolizumab (111758.9 ± 43622.0 US dollars/year vs 292697.1 ± 214854.0 US dollars/year; P = 0.049; Figure 2d).

A total of 13 studies compared the economic evaluation of Pembrolizumab grouped by the PD-L1 expression (Table 3), in which nine studies were from the United States payer perspective and four from the Chinese payer perspective. The gained QALY (2.3 ± 0.5 vs 2.2 ± 0.6 years; P = 0.729; Figure 3a), incremental QALY (0.99 ± 0.41 vs 0.93 ± 0.43 years; P = 0.759; Figure 3b), cost increment (86787.2 ± 50,792.6 vs 83278.9 ± 40,328.6 US dollars; P = 0.853; Figure 3c), and ICER (92761.6 ± 46,501.6 vs 106592.8 ± 56,454.1 US dollars/year; P = 0.502; Figure 3d) were all comparable between the PD-L1 expression ≥50% and 1–49%.

Thirteen (43.3%) analyses of the eight studies were enrolled in our pooled analyses of subgroup analyses of the PD-L1 expression, and the sole study for Atezolizumab was not incorporated in our further analysis. It showed that the ICER was lower than WTP in 43% of the included cost-effectiveness analyses, and the ratio was 54.5% (n = 12) and 12.5% (n = 1) for Pembrolizumab and Atezolizumab, respectively. There was no significant difference between ICER and WTP either for Pembrolizumab (111759 vs 122336 US dollars; P = 0.533) or Atezolizumab (292697.1 vs 117362 US dollars; P = 0.056) among the 30 cost-effectiveness analyses. As for Pembrolizumab, the ICER and WTP were comparable in the Chinese payer perspective (74945 vs 44870 US dollars; P = 0.193), while the ICER was significantly inferior to WTP in the US payer perspective (135091 vs 172138 US dollars; P = 0.017). The ICER and WTP were comparable in the US payer perspective for Atezolizumab (388976 vs 136000 US dollars; P = 0.063).

There were 23 studies (92%) that reported the one-way sensitivity analysis and the extrapolation/utility of overall survival/progression-free survival and total cost of immune checkpoint inhibitors were the main sensitive factors. Among

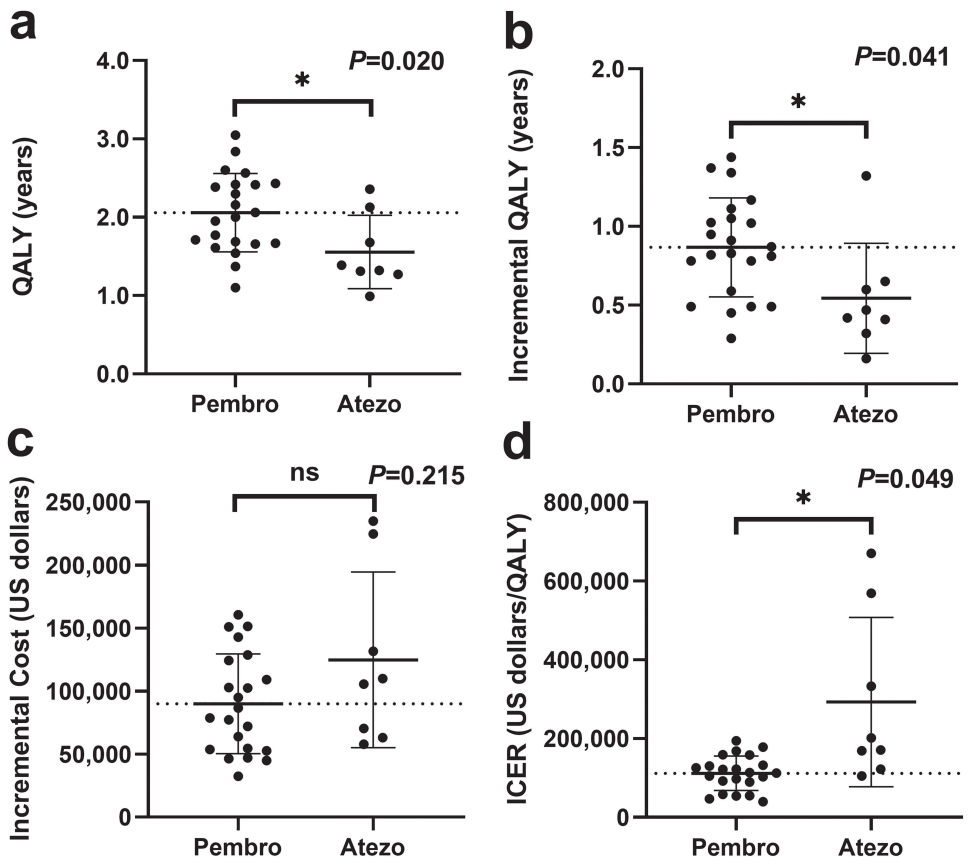

Figure 2 The variance of quality-adjusted life years (**a**), incremental quality-adjusted life years (**b**), increment cost compared to chemotherapy (**c**), and incremental cost-effectiveness ratio (**d**) between Pembrolizumab and Atezolizumab. The asterisk indicator, statistically significant difference (*P*-value < 0.05).
Abbreviations: QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; ns, not significant.

the eight studies on Atezolizumab, six reported the outcomes of sensitivity analysis, and five showed that the cost of Atezolizumab was the critical sensitive factor.

We then check the quality of the included cost-effectiveness analyses conforming to the CHEERS checklist (Figure 4). After a systematic review in accordance with the CHEERS checklist, it revealed a high quality of these included studies. The report of characterizing heterogeneity (56%) and approach (16%) and effect (12%) to engagement with patients and others affected by the study were not satisfactory, while all studies met at least 23 criteria for this checklist.

Table 3 The Economic Metrics of the Total Population Who Received Pembrolizumab or Atezolizumab, and the Economic Metrics of Those with Pembrolizumab Stratified by PD-L1 Expression

Characteristics	Pembrolizumab	Atezolizumab	P-value	Pembrolizumab		
				TPS≥50%	TPS 1–49%	P-value
Cost increment	89883.4 ± 39,644.8	124,720.3 ± 69,709.1	0.215	86,787.2 ± 50,792.6	83,278.9 ± 40,328.6	0.853
QALY	2.1 ± 0.5	1.6 ± 0.5	0.020	2.3 ± 0.5	2.2 ± 0.6	0.729
QALY increment	0.87 ± 0.31	0.54 ± 0.35	0.041	0.99 ± 0.41	0.93 ± 0.43	0.759
ICER	111758.9 ± 43,622.0	292,697.1 ± 214,854.0	0.049	92,761.6 ± 46,501.6	106,592.8 ± 56,454.1	0.502
WTP	122336.1 ± 65,611.0	117,362.8 ± 46,437.1	0.820			

Abbreviations: TPS, tumor proportion score; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; WTP, willingness to pay.

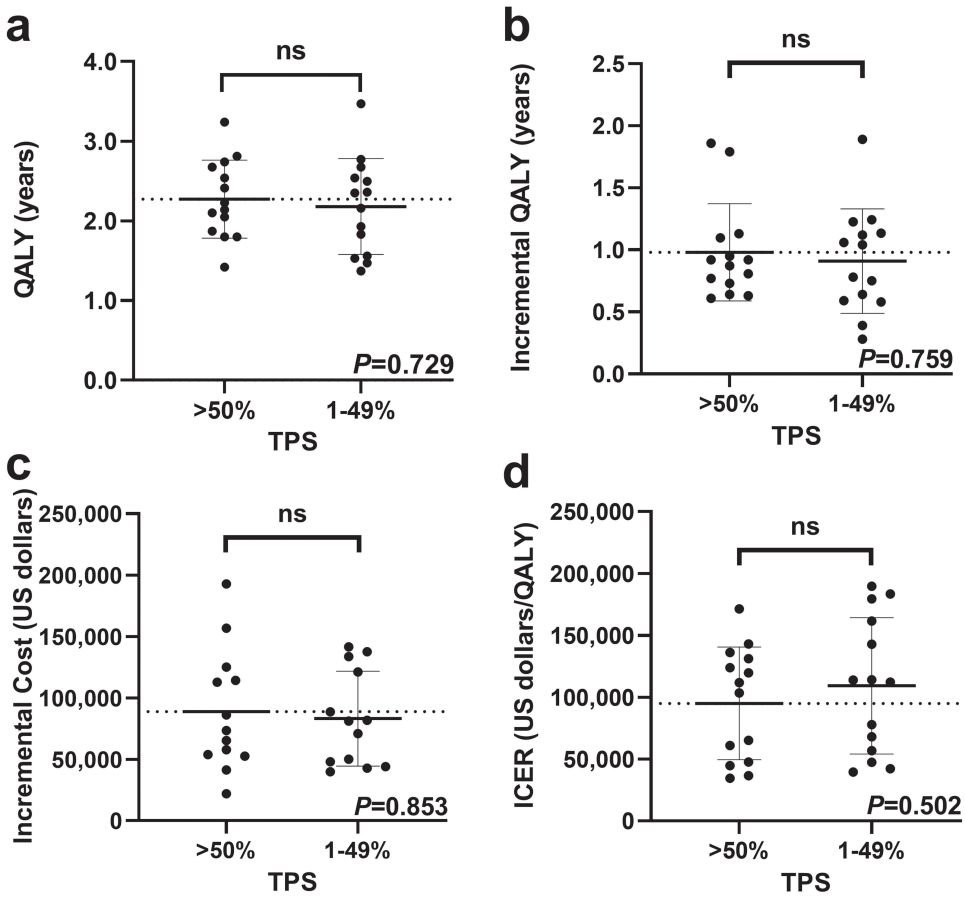

Figure 3 The variance of quality-adjusted life years (**a**), incremental quality-adjusted life years (**b**), increment cost compared to chemotherapy (**c**), and incremental cost-effectiveness ratio (**d**) of Pembrolizumab between tumor proportion score ≥50% and 1–49%.

Abbreviations: QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; TPS, tumor proportion score; ns, not significant.

Discussion

Immunotherapy brought unprecedented survival benefits for patients with advanced or metastatic NSCLC, while the financial burden came together with the prognosis improvements.[2–4] The financial toxicity would not be neglected due to the extremely high cost that it might prevent the continuation of effective medical treatment. Previous research would care more about the absolute survival benefits, while there were no perspectives on the directional opinions of cost-effectiveness analysis on the clinical decision of immunotherapy.[2,40] In our research, we conducted a systematic review of economic evaluations on those with advanced or metastatic NSCLC who received Pembrolizumab or Atezolizumab. The comparisons between WTP and ICER suggested that ICIs would lead to financial toxicity in those patients, despite the countries and study patients. The impact of financial toxicity would vary for study drugs, target patient population, and study countries. Thus, the integration of financial toxicity assessment during the process of clinical decision might help patients identify the potential financial toxicity in advance and better arrange the medical treatment for more benefits.

Nowadays, Pembrolizumab and Atezolizumab are considered the first-line treatment for metastatic NSCLC,[41,42] while current research would commonly compare the absolute survival benefit of the medical treatment. Our findings suggested that Pembrolizumab was associated with comparable cost and better QOL-related prognosis than Atezolizumab, and Pembrolizumab showed distinct cost-effectiveness for its lower ICER. Even though the ICER was comparable with WTP for either Pembrolizumab or Atezolizumab in statistical significance, the absolute mean value of the ICER of Atezolizumab was two times higher than its WTP. Atezolizumab was also found lack of cost-effectiveness in other research.[34] Considering the heterogeneity of the included study amount, the comparison results between ICER and

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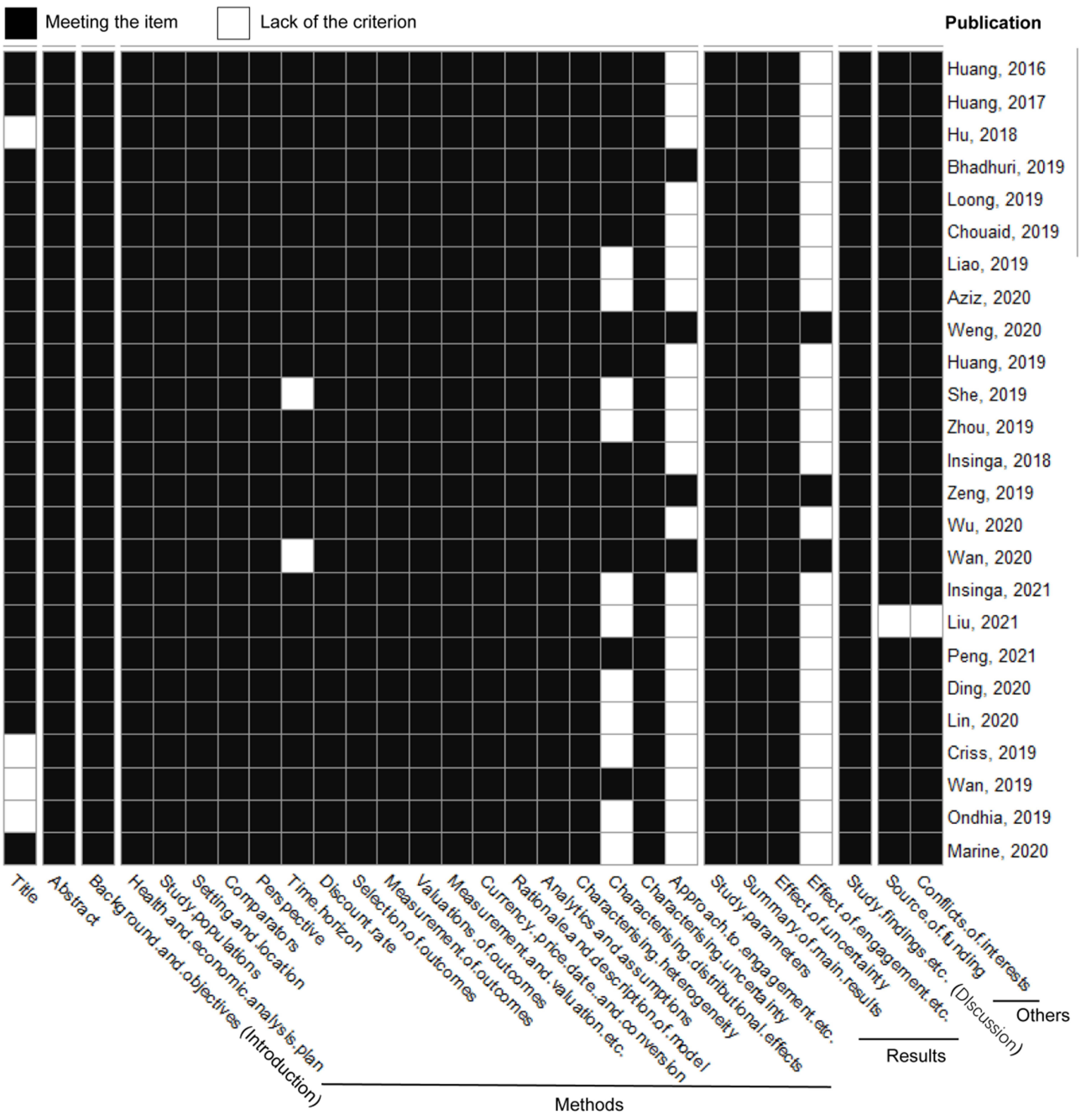

Figure 4 The heatmap to show whether each included study met the standards of quality assessment (the Consolidated Health Economic Evaluation Reporting Standards checklist), in which the black square was referred to as meeting the item, and the white square represented the lack of this criterion.

Abbreviations: Measurement and valuation, etc., measurement and valuation of resources and costs; approach to engagement, etc., approach to engagement with patients and others affected by the study; effect of engagement, etc., the effect of engagement with patients and others affected by the study; study findings, etc., study findings, limitations, generalisability, and current knowledge.

WTP for Atezolizumab tended to be interpreted carefully. Additionally, as stratified by the countries, Pembrolizumab demonstrated significant cost-effectiveness in the US (P = 0.017) and was acceptable in China (P = 0.193). Due to the limited involved studies on Atezolizumab, we merely conducted the analyses for the US. It seemed to show the tendency of higher ICER than WTP (P = 0.063), while the absolute difference between the two values was nearly two times the WTP. Therefore, these results reminded us of the high cost-effectiveness of Pembrolizumab in those with advanced or metastatic NSCLC.

Furthermore, we might not overlook the treatment duration setting in the sensitivity analysis, which might result in an inconsistent outcome for ICER. There were no more than five years for the duration (including the extrapolation of overall survival) in the sensitivity analysis of three studies for Atezolizumab.[35,37,38] As concerned by Ondhia, the Economic Guidance Panel reduced the horizon time from ten years to five years in their analyses, which might lead to a conservative cure rate of Atezolizumab and potentially shortened QALY. The concurrent changes would result in an illusory enhanced ICER for Atezolizumab; thus, a longer follow-up of the study population might help disclose the actual improved QALY.[35] Moreover, the summary from these one-way sensitivity analyses suggested that apart from improving overall survival or progression-free survival, the total cost of the study drugs is also considered the critical sensitive factor, which would impact the cost-effectiveness of Atezolizumab. In this way, besides the prognosis improvement, the reduction of the total cost was the first and essential approach to attenuate financial toxicity without a doubt.

The PD-L1 expression was a critical indicator for clinical decision and prognosis evaluation,[43] while our findings revealed that the prognosis and economic parameters seemed unrelated to the PD-L1 expression for those with Pembrolizumab, including the QALY, total cost, and ICER. However, our findings seemed to be contrary to the prior research that the enrichment of PD-L1 was associated with improved survival and enhanced value.[6] We deemed that the satisfactory survival improvement in the early and limited research might be a confounding factor for the QALY and ICER estimation. A global, real-world, multicenter study proposed that the PD-L1 expression of nearly one-third of the enrolled patients (n = 702; 30%) was 1–49% and 22% (n = 530) was ≥50% among those with advanced or metastatic NSCLC.[44] Considering the improved survival of Pembrolizumab among the metastatic NSCLC with low PD-L1 expression levels,[40] Pembrolizumab was strongly recommended regardless of the PD-L1 expression level due to the comparable QOL-associated prognosis and economic evaluations. Since tumor mutation burden (TMB) was recommended as the immune biomarker,[45,46] TMB might also act as a second stratification factor in further cost-effectiveness analyses.

The involved cost-effectiveness analyses were studies in developed countries except for China, and all studies for the UK, Singapore, and Canada showed no cost-effectiveness of the ICIs. We reasonably speculated that the financial toxicity might also appear in other countries, and it was supposed to be considered in clinical practice and provide mitigating strategies actively.[4] To our knowledge, this is the first study to explore the role of financial toxicity in the clinical decision of immunotherapy, yet our study has some limitations. First, since the cost of ICIs could be covered by the health care system and patients themselves, the precise financial burden of patients might vary from the geographic region, which could result in bias in calculating the total cost.[4,47] Second, we could notice the heterogeneity of cost-effectiveness analysis conclusions between the general patients and those pertaining to the early-reported clinical trials. That we merely included the studies with high evidence grade could lead to high reliability, while it might result in inherent blemish for the data from clinical trials. As suggested by the previous study, the favored findings in the cost-effectiveness analyses from the partial latest report might be confounded by the model assumptions and could be interpreted as an extraordinarily improved survival with comparatively limited follow-up.[25] In this way, further cost-effectiveness analyses might be inclined to the real-world study, which might help to uncover the general performance of financial toxicity on the suffered patients. Third, there was an inherent bias in the current cost-effectiveness analyses that the setting of WTP did not reach a consensus. A study drug with the same price in two countries might lead to a contrary conclusion on whether it was cost-effective or lack of cost-effectiveness. That is, setting a WTP threshold might mislead to a different interpretation of the economic evaluations. Taking China as an example, considering financial toxicity, patients in clinical practice tend to prioritize the cost of drugs when their efficacy is comparable, opting for those with lower financial toxicity. Most targeted therapies have been included in NRDL. In contrast, immune checkpoint inhibitors are not yet covered by China's drug policies, remaining priced above WTP threshold and posing significant financial toxicity. For advanced NSCLC without driver gene mutations, immunotherapy is often the preferred option, but it is associated with considerable financial toxicity.

Conclusions

Immune checkpoint inhibitors would lead to financial toxicity in patients with advanced or metastatic lung cancer from various countries, and the impact of financial toxicity differed for the study drugs, target patient population, and study

countries. The integration of financial toxicity assessment during clinical decision would help these patients get more benefits in the whole course of immunotherapy.

Key Statements

1. Immune checkpoint inhibitors would lead to financial toxicity across countries.
2. The impact of financial toxicity differed for the study drugs and patient population.
3. Integrating financial toxicity assessment could be profitable during immunotherapy.

Data Sharing Statement

We used publicly available summary-level data, and more details could be available from the corresponding authors.

Ethics Approval

The Ethics Committee of Sichuan University West China Hospital waived the research ethics approval due to the systematic review of published studies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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