Original Article

Personal and clinical characteristics associated with immunotherapy effectiveness in stage IV non-small cell lung cancer

Krishna H. Patel[1], Naomi Alpert[1], Stephanie Tuminello[2], Emanuela Taioli[1,3]

[1]Institute for Translational Epidemiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]NYU Grossman School of Medicine, New York, NY, USA; [3]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Contributions: (I) Conception and design: KH Patel, E Taioli; (II) Administrative support: KH Patel, N Alpert; (III) Provision of study materials or patients: E Taioli; (IV) Collection and assembly of data: KH Patel, N Alpert, E Taioli; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Emanuela Taioli, MD, PhD. Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1133, New York, NY 10029, USA. Email: emanuela.taioli@mountsinai.org.

Background: Immunotherapy response rates in metastatic non-small cell lung cancer (NSCLC) are low and survival varies significantly. Factors like age, sex, race, and histology may modulate immunotherapy response. Existing analyses are limited to clinical trials, with limited generalizability, and meta-analyses where adjustment for potential confounders cannot be performed. Here, we conduct a cohort study with patient-level analysis to explore how personal and clinical characteristics moderate chemoimmunotherapy effectiveness in metastatic NSCLC.

Methods: Stage IV NSCLC patients diagnosed in 2015 were drawn from Surveillance Epidemiology, and End Results-Medicare linked data. Receipt of chemoimmunotherapy and overall survival (OS) were the primary predictor and outcome of interest respectively. Multivariable Cox-proportional hazards regression and propensity-score matching were performed to evaluate the effectiveness of immunotherapy addition to chemotherapy.

Results: From a total of 1,471 patients, 349 (24%) received chemoimmunotherapy and 1,122 (76%) received chemotherapy alone. Survival was significantly better among those treated with chemoimmunotherapy compared to those receiving chemotherapy alone [adjusted hazard ratio (HR_{adj}) =0.72, 95% confidence interval (CI): 0.63–0.83]. Males saw significantly better OS from chemoimmunotherapy (HR_{adj} =0.62, 95% CI: 0.51–0.75) than females (HR_{adj} =0.81, 95% CI: 0.65–1.01, $P_{interaction}$=0.0557). After propensity-score matching, the effect of chemoimmunotherapy was borderline significant according to sex ($P_{interaction}$ =0.0414), but not age or histology.

Conclusions: Males may benefit more from chemoimmunotherapy, but there is limited evidence suggesting age, histology, race, and comorbidities contribute to differences in effectiveness. Future research should elucidate who responds best to chemoimmunotherapy, and further analyses of characteristics like race can inform how to tailor different treatment regimens to distinct patient subpopulations.

Keywords: Metastatic non-small cell lung cancer (metastatic NSCLC); immunotherapy; survival outcomes; disparities

Submitted Sep 22, 2022. Accepted for publication Feb 03, 2023. Published online Jun 13, 2023.
doi: 10.21037/tlcr-22-682
View this article at: https://dx.doi.org/10.21037/tlcr-22-682

Introduction

Immunotherapy has radically altered the landscape of treatment for non-small cell lung cancer (NSCLC), especially for those diagnosed with late-stage disease. Each year in the United States approximately 130,000 late-stage NSCLC patients receive some form of immunotherapy treatment (1). Commonly used immunotherapy agents for NSCLC include immune checkpoint inhibitors (ICIs) pembrolizumab, nivolumab, and atezolizumab (2). These drugs inhibit either the programmed cell death protein 1 (PD-1) located on T-cells, or programmed cell death ligand 1 (PD-L1) proteins located on tumor cells, to halt the immune response (3). Pembrolizumab is an anti-PD-1 agent that was FDA approved for first and second-line use in patients with metastatic NSCLC in 2015, and first-line treatment in patients with unresectable, stage III tumors in 2019 (4,5). Nivolumab (anti-PD-1) is approved for second-line use independent of PD-L1 expression, and atezolizumab (anti-PD-L1) is a second-line treatment but has first-line efficacy in patients with high PD-L1 expression (6). Recent clinical trials support the efficacy of various combinations of ICI plus platinum-based chemotherapy for advanced- stage NSCLC. As of 2020, both pembrolizumab and nivolumab have been approved in combination with chemotherapy for first-line treatment of patients with late-stage NSCLC (7). Although median overall survival (OS) for late-stage NSCLC patients receiving immunotherapy-chemotherapy combination treatment (chemoimmunotherapy) ranges between 12–22 months compared to 7–11 months for those receiving chemotherapy only (8,9), objective response rates vary significantly, and are as low as 41% (10), 19% (11), and 15% (12) for pembrolizumab, nivolumab, and atezolizumab, respectively.

Because not all NSCLC patients experience benefit from immunotherapy, this suggests that there are factors modulating immunotherapy response. However, the extent to which various personal characteristics such as age, sex, and race contribute to these differential outcomes is not well understood, especially in the presence of clinical characteristics that can act as confounders. Emerging research suggests that demographic and behavioral factors modify the effect of immunotherapy (13). A meta-analysis of randomized-control trials (RCTs) that compared single-agent immunotherapy to chemotherapy found ever-smokers had significant increases in OS while never-smokers did not (14). The authors also concluded single-agent immunotherapy may have limited effectiveness for elderly patients as the first-line of treatment (14). In a separate systematic review, evidence was mixed, but males, younger patients, and smokers were more frequently observed to derive survival benefit from immunotherapy-based treatments (15). However, systematic reviews and meta-analyses do not permit for adjustment of patient-level characteristics, and the majority of clinical trials examining these questions often over-enroll younger, male, and healthier patients who may not be representative of the broader NSCLC population, thus the results have limited external validity.

As such, findings from patient level analysis of large datasets may produce more generalizable findings than RCTs. However, most existing observational studies do not include non-immunotherapy control groups. Therefore, we used the Surveillance, Epidemiology and End Results (SEER)-Medicare dataset to assess whether chemotherapy-immunotherapy combination treatment (chemoimmunotherapy) increases survival in a large, population-based dataset and to explore whether personal and clinical characteristics moderate the effectiveness of chemoimmunotherapy in NSCLC patients with metastatic disease. SEER-Medicare includes detailed information about demographics, clinical and tumor characteristics, and treatment, allowing for patient-level adjustment, with results more representative of real-world patient experiences and clinical practice. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-682/rc).

Highlight box

Key findings

- Males may receive more benefit from chemoimmunotherapy than female non-small cell lung cancer (NSCLC) patients.

What is known and what is new?

- Stage IV NSCLC has a very poor prognosis, and responses to immunotherapy are highly variable across patients.
- Randomized-controlled trials are not generalizable to real world patient experiences, and reporting of outcomes and covariate adjustments differ across studies.
- This study uses patient-level analysis of a national database to yield more generalizable, population-based findings, including reporting of outcomes by race which is very limited in previous literature.

What is the implication, and what should change now?

- Future research should investigate mechanisms between sex and immunotherapy response as well as other personal characteristics like race which have been traditionally underreported.

Methods

Data source and selection criteria

This cohort was derived from the SEER-Medicare linked data. SEER includes cancer incidence and mortality data from population-based registries covering approximately 35% of the United States population (16). Medicare includes healthcare claims information for beneficiaries, with eligibility starting at age 65 years. Patients with a microscopically first or only primary confirmed diagnosis of stage IV NSCLC from 1992 to 2015 were extracted from the dataset (n=127,403). In order to capture comorbidities from claims prior to diagnosis and treatments after diagnosis, patients were limited to those at least 66 years old at diagnosis (20,828 patients excluded) with continuous Part A and B coverage and no Part C coverage, for 1 year prior to and 1 year post diagnosis (or until death) (n=28,887 additional patients excluded). The sample was limited to those diagnosed in 2015, the latest available year, based on FDA approval of immunotherapy for lung cancer (pembrolizumab was first approved for NSCLC in 2015) and the availability of billing codes (n=45,826 additional patients excluded). Patients who received chemotherapy, with or without the addition of immunotherapy, based on Healthcare Procedural Coding System (HCPCS) codes (Table S1), as part of their care were included in the study cohort (n=1,471) (Figure S1).

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Mount Sinai School of Medicine, in accordance with Mount Sinai's Federal Wide Assurances (FWA#00005656, FWA#00005651) and a waiver of informed consent was obtained for all patients as part of the IRB application.

Variables of interest

The primary predictor was receipt of chemoimmunotherapy and the primary outcome was OS. Receipt of immunotherapy was binarily defined based on the presence of HCPCS codes for approved PD-1/PD-L1 inhibitors—atezolizumab, nivolumab, and pembrolizumab in a patient's claims in the year after diagnosis (Table S1), regardless of the order in which the chemotherapy and immunotherapy were administered. Survival was calculated from date of diagnosis and was complete through December 31, 2017; follow up was limited to 2 years, the longest time available for all patients.

Data on age at diagnosis, sex, race, histology, and marital status were extracted from SEER. Race was categorized as white, Black, or Other. Marital status was classified as married (including domestic partnerships) or unmarried (including never married, divorced, and widowed). Tumor histology was classified as squamous cell carcinoma, adenocarcinoma, or other based on codes from the International Agency for Cancer Research (IARC) (17,18). Charlson Comorbidity Index (CCI) scores were extracted from Medicare claims, based on a modified version of the NCI CCI that incorporated ICD-10 codes (19,20). Specifically, the CCI is comprised of the following comorbidities, all of which are associated with treatment response and overall health: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident or transient ischemic attack, chronic obstructive pulmonary disease, peptic ulcer disease, paralysis or hemiplegia, diabetes history, liver disease, and kidney disease—the last three of which are further weighted by severity (19,20).

Statistical analysis

Chemoimmunotherapy and immunotherapy patients were compared on demographic and clinical characteristics, using χ^2 tests. Multivariable logistic regression was conducted to identify factors independently associated with receipt of chemoimmunotherapy. Kaplan-Meier curves and the log-rank test were used to assess differences in the 2-year OS according to treatment. Multivariable Cox-proportional hazards regression models were performed to evaluate the independent association of chemoimmunotherapy treatment with OS, adjusting for age, sex, race, marital status, comorbidities, and histology. Survival analyses were stratified on variables with a significant independent association with survival, and interaction terms were assessed to examine differences in effectiveness of chemoimmunotherapy across strata. Multivariable analyses were conducted on the subset of patients with complete data for all variables. A sensitivity analysis was also performed on the subgroup of patients with available data on brain metastasis at time of diagnosis (n=1,402).

Differences in OS were also assessed using a 1:1 propensity matched analysis, matching on all covariates, and using the optimal matching option in the MATCHIT package in R (21). For variables with evidence of an interaction with chemoimmunotherapy in the multivariable model (interaction term P<0.1), stratified propensity score matching analyses were conducted to assess interaction

Table 1 Description of the study sample according to treatment

Variables	Chemotherapy only (n=1,122), n (%)	Chemoimmunotherapy (n=349), n (%)	P value
Age at diagnosis, years			0.1213
66–69	300 (26.7)	109 (31.2)	
70–74	345 (30.7)	100 (28.7)	
75–79	273 (24.3)	92 (26.4)	
≥80	204 (18.2)	48 (13.7)	
Sex			0.6399
Male	598 (53.3)	191 (54.7)	
Female	524 (46.7)	158 (45.3)	
Race			0.1746
White	983 (87.6)	306 (87.7)	
Black	93 (8.3)	22 (6.3)	
Other	46 (4.1)	21 (6.0)	
Marital status			0.0436
Unmarried	427 (38.1)	117 (33.5)	
Married/domestic partner	664 (59.2)	214 (61.3)	
Unknown	31 (2.7)	18 (5.2)	
Charlson Comorbidity Index			<0.0001
0	454 (40.5)	152 (43.6)	
1	301 (26.8)	124 (35.5)	
2	187 (16.7)	39 (11.2)	
≥3	180 (16.0)	34 (9.7)	
Histology			0.0875
Adenocarcinoma	713 (63.5)	209 (59.9)	
Squamous cell carcinoma	255 (22.7)	99 (28.4)	
Other	154 (13.7)	41 (11.7)	

terms (22). Two-sided P values <0.05 were deemed statistically significant in final interpretations of analyses. All analyses were conducted in R Studio Version 3.6.1.

Results

Patient characteristics

Of the 1,471 patients with stage IV NSCLC meeting selection criteria, 1,122 (76%) received chemotherapy alone and 349 (24%) received chemoimmunotherapy. Patients receiving chemoimmunotherapy were more likely to be married (61.3% *vs.* 59.2%, P=0.0436) and have fewer comorbidities (43.6% with CCI 0, *vs.* 40.5%, P<0.0001) than those receiving chemotherapy alone (*Table 1*). After adjustment, those with adenocarcinoma were less likely to receive immunotherapy [adjusted odds ratio (OR_{adj}) =0.73, 95% confidence interval (CI): 0.54–0.98], compared to those with squamous cell carcinoma, as were those with a CCI score of at least 2, compared to those with a CCI score of 0 (CCI 2, OR_{adj} =0.63, 95% CI: 0.42–0.94; CCI ≥3, OR_{adj} =0.53, 95% CI: 0.34–0.80) (*Table 2*).

Table 2 Factors associated with receipt of chemoimmunotherapy versus chemotherapy

Variables	OR (95% CI), n=1,471	OR_{adj} (95% CI), n=1,422[†]
Age at diagnosis, years		
66–69	1.0 (ref)	1.0 (ref)
70–74	0.80 (0.58–1.09)	0.79 (0.57–1.09)
75–79	0.93 (0.67–1.28)	0.88 (0.63–1.24)
≥80	0.65 (0.44–0.95)	0.70 (0.47–1.03)
Sex (female *vs.* male)	0.94 (0.74–1.20)	1.00 (0.77–1.30)
Race		
White	1.0 (ref)	1.0 (ref)
Black	0.76 (0.46–1.21)	0.79 (0.47–1.29)
Other	1.47 (0.85–2.46)	1.45 (0.82–2.49)
Marital status (married *vs.* unmarried)	1.18 (0.91–1.52)	1.21 (0.92–1.59)
Charlson Comorbidity Index		
0	1.0 (ref)	1.0 (ref)
1	1.23 (0.93–1.62)	1.26 (0.95–1.68)
2	0.62 (0.41–0.91)	0.63 (0.42–0.94)
≥3	0.56 (0.37–0.84)	0.53 (0.34–0.80)
Histology		
Squamous	1.0 (ref)	1.0 (ref)
Adenocarcinoma	0.76 (0.57–1.00)	0.73 (0.54–0.98)
Other	0.69 (0.45–1.03)	0.69 (0.44–1.05)

[†], adjusted for age, sex, race, marital status, Charlson Comorbidity status, histology (all of the above variables), 49 patients excluded because marital status missing/unknown.

Survival

Survival was significantly (P<0.0001) better among those who received chemoimmunotherapy [median 14.8 (IQR, 10.4–23.3) months] than for those who received chemotherapy alone [median 9.2 (IQR, 4.8–21.6) months] (*Figure 1A*), and remained so after adjusting for potential confounders [adjusted hazard ratio (HR_{adj}) =0.72, 95% CI: 0.63–0.83). Female sex was independently associated with better OS, while older age and non-adenocarcinoma histologies were independently associated with worse OS (*Table 3*).

When multivariable survival analyses were stratified by sex, age, and histology, chemoimmunotherapy significantly increased survival in males (HR_{adj} =0.62, 95% CI: 0.51–0.75), but not in females (HR_{adj} =0.81, 95% CI: 0.65–1.01, $P_{interaction}$=0.0557). Likewise, chemoimmunotherapy treatment among older age groups was associated with significantly better survival (age 70–74 years, HR_{adj} =0.67, 95% CI: 0.52–0.88; age 75–79 years, HR_{adj} =0.72, 95% CI: 0.54–0.96; age ≥80 years, HR_{adj} =0.55, 95% CI: 0.39–0.80). However, there was no significant interaction between age and receipt of chemoimmunotherapy ($P_{interaction}$=0.2615). All histologies saw better survival with chemoimmunotherapy (squamous, HR_{adj} =0.67, 95% CI: 0.51–0.88; adenocarcinoma, HR_{adj} =0.82, 95% CI: 0.68–0.99; other, HR_{adj} =0.47, 95% CI: 0.31–0.72; $P_{interaction}$=0.0695) (*Table 4*).

After propensity matching, the cohort was well balanced on all covariates [all standardized mean difference (SMD) <0.1] and there remained a consistent survival benefit with chemoimmunotherapy, compared to chemotherapy alone (HR =0.72, 95% CI: 0.60–0.85) (*Figure 1B*).

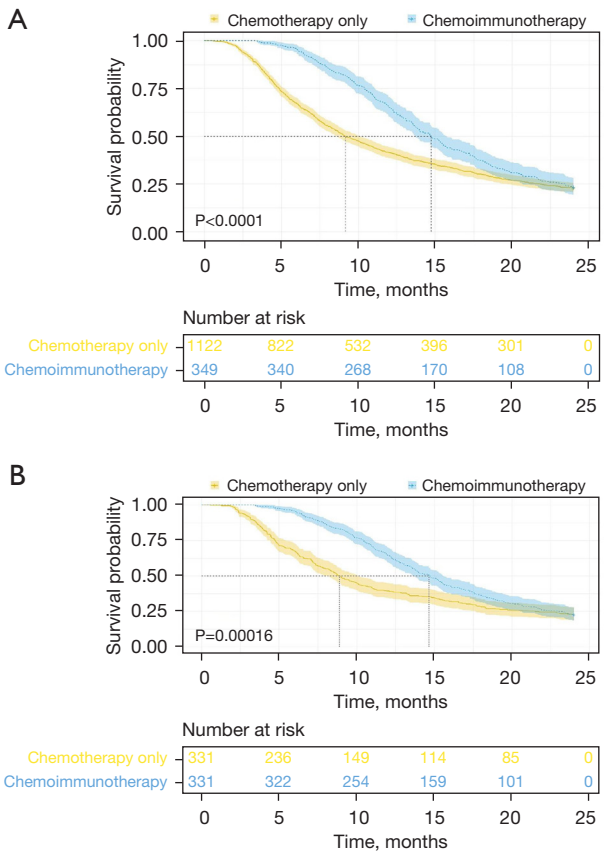

Figure 1 Overall survival according to treatment in the (A) overall cohort (n=1,471); (B) the propensity matched cohort (n=662).

Stratified propensity-matches were performed by sex and histology and were well balanced on all covariates (all SMD <0.1). Chemoimmunotherapy showed a borderline significant survival increase over chemotherapy among males, but not females (male, HR =0.59, 95% CI: 0.47–0.74; female, HR =0.85, 95% CI: 0.65–1.12; $P_{interaction}$=0.0414) (Figure S2, Table S2). Patients with squamous-cell (HR =0.71, 95% CI: 0.54–0.95) and "Other" histology (HR =0.52, 95% CI: 0.31–0.88) had significantly better OS with chemoimmunotherapy than with chemotherapy alone, but patients with adenocarcinoma (HR =0.91, 95% CI: 0.73–1.15) did not, although there was no statistical interaction between histology and receipt of chemoimmunotherapy ($P_{interaction}$=0.1655) (Table S2).

A sensitivity analyses was performed to further adjust for presence of brain metastasis at diagnosis. Chemoimmunotherapy treatment was still associated with significantly better survival (chemoimmunotherapy *vs.* chemotherapy alone, HR_{adj} =0.72, 95% CI: 0.63–0.83). Brain metastasis at diagnosis (HR_{adj} =1.41, 95% CI: 1.22–1.63) as well as a CCI ≥3 (HR_{adj} =1.21, 95% CI: 1.01–1.46) and "Other" histology (HR_{adj} =1.34, 95% CI: 1.10–1.63) were found to be independently associated with shorter OS (Table S3). Otherwise, all other results from the sensitivity analysis were consistent with the original multivariate model. For instance, female patients (sex, HR_{adj} =0.73, 95% CI: 0.64–0.83) still had significantly better survival with chemoimmunotherapy and those over age 80 years (HR_{adj} =1.28, 95% CI: 1.07–1.54) had lower OS with chemoimmunotherapy (Table S3).

Table 3 Factors independently associated with mortality

Variables	HR_{adj} (95% CI), n=1,422[†]
Chemoimmunotherapy *vs.* chemotherapy alone	0.72 (0.63–0.83)
Age at diagnosis, years	
66–69	1.0 (ref)
70–74	1.03 (0.88–1.21)
75–79	1.08 (0.91–1.28)
≥80	1.29 (1.08–1.55)
Sex (female *vs.* male)	0.74 (0.65–0.84)
Race	
White	1.0 (ref)
Black	0.81 (0.65–1.02)
Other	0.81 (0.60–1.09)
Marital status (married *vs.* unmarried)	0.90 (0.79–1.03)
Charlson Comorbidity Index	
0	1.0 (ref)
1	1.01 (0.87–1.17)
2	0.97 (0.81–1.16)
≥3	1.16 (0.97–1.39)
Histology	
Squamous	1.0 (ref)
Adenocarcinoma	0.89 (0.77–1.02)
Other	1.34 (1.10–1.63)

[†], adjusted for age, sex, race, marital status, Charlson Comorbidity status, histology (all of the above variables), 49 patients excluded because marital status missing/unknown. CI, confidence interval.

Table 4 Association of chemoimmunotherapy with survival according to sex, age, histology

Strata	HR_{adj} (95% CI), chemoimmunotherapy *vs.* chemotherapy alone	P value (strata*receipt of chemoimmunotherapy interaction)
Sex		0.0557
Male (n=765)	0.62 (0.51–0.75)	
Female (n=657)	0.81 (0.65–1.01)	
Age at diagnosis, years		0.2615
66–69 (n=394)	0.83 (0.63–1.08)	
70–74 (n=431)	0.67 (0.52–0.88)	
75–79 (n=353)	0.72 (0.54–0.96)	
≥80 (n=244)	0.55 (0.39–0.80)	
Histology		0.0695
Squamous (n=346)	0.67 (0.51–0.88)	
Adenocarcinoma (n=886)	0.82 (0.68–0.99)	
Other (n=190)	0.47 (0.31–0.72)	

Adjusted for age, sex, and histology. CI, confidence interval.

Discussion

Overall, chemoimmunotherapy was found to yield significantly better OS compared to chemotherapy in a population-based sample, consistent with results widely reported in RCTs. In the overall and propensity-matched patient cohorts, chemoimmunotherapy yielded significant increases in OS over chemotherapy for males but not females, with a statistically significant interaction. These findings may indicate that male NSCLC patients derive greater benefit from the addition of immunotherapy than females do.

There is conflicting evidence around sex-based differences in response to immunotherapy. Conforti *et al.*'s pooled meta-analysis [2018] of both single-agent and chemoimmunotherapy treatments across all metastatic cancers concluded the difference in immunotherapy effectiveness across sex was significant, with male patients experiencing a greater magnitude of benefit (23). Likewise, the CheckMate 227 (24) and KEYNOTE 042 (25) clinical trials comparing immunotherapy to chemotherapy in first-line metastatic disease found that male patients had a significant increase in OS from immunotherapy while females did not. In contrast, a second, separate meta-analysis by Conforti *et al.* [2019] comparing anti-PD-L1 chemoimmunotherapy to chemotherapy alone found female patients with advanced NSCLC derived a greater marginal benefit in OS from chemoimmunotherapy than men (26). Moreover, female but not male patients saw significantly better OS with immunotherapy in the IMPower130 trial comparing chemoimmunotherapy to chemotherapy in first-line treatment (27). Our systematic review [2022] found that experimental studies tended to show better survival with immunotherapy in male patients, while data for female patients was less conclusive, although females consistently showed better survival than males in terms of the absolute number of lived months (15). One hypothesis offered for this discrepancy was that males may derive greater marginal benefit from immunotherapy than females, but not enough to cover pre-existing female patients' survival advantage (15).

While biological mechanisms explaining sex-based differences in immunotherapy response have not been fully established, estrogen and testosterone stimulate immunogenic and immunosuppressive activity respectively through their influence on the immune system and gene expression (28,29). β-estradiol in particular has been associated with a pro-tumor microenvironment through enhancement of pro-tumor infiltrating lymphocytes and concomitant suppression of anti-tumor immune cells (30). Women are also more likely to have EGFR, ALK, or ROS mutations, all of which are associated with worse survival when they occur concomitantly (31). Additionally, population-based cohort studies suggest male patients are generally more likely to be smokers than female patients, and

are also more likely to experience occupational exposures, which may result in higher tumor mutation burden (up to tenfold higher), increased immunogenicity, and more tumor cell recognition by the immune system (32,33). Published literature also shows better survival in smokers with stage IV NSCLC treated with immunotherapy (13-15). Specifically, a recent systematic review found that of 15 experimental studies and 13 observational studies reporting OS according to smoking status, eight and seven studies respectively showed better survival in ever-smokers compared to never-smokers treated with immunotherapy (15).

Findings concerning age have also been inconsistent in the broader literature. Most RCTs suggest younger patients derive more immunotherapy benefit than older patients (34,35), possibly due to numerous mechanisms including dampened intrinsic immunity, immunosenescence, and heightened sensitivity to carcinogens (36,37). We conducted a systematic review [2022], and found that overall, for patients aged 75 and older, immunotherapy often provided statistically insignificant marginal survival benefit over other treatments, while the majority of published experimental and observational studies demonstrated significant survival improvement in patients younger than 75 years treated with immunotherapy (15). Moreover, a meta-analysis by Raphael *et al.* [2020] found patients older than 65 years only saw better OS with immunotherapy as second-line treatment but not as first-line treatment (14). Although the overall interaction between age and immunotherapy was not significant with respect to differences in effectiveness, the oldest patients (i.e., those >80 years) in our study cohort were significantly less likely to receive immunotherapy. However, the few over-80 patients (n=48) who did receive immunotherapy saw significant increase in OS, while patients aged 66–69 years did not, contrary to findings of Raphael *et al.* [2020] (14). It is possible that these results reflect physician choice, as chemoimmunotherapy may have only been prescribed to patients over 80 years if they were suspected to display a strong immunotherapy response.

Although the interaction was not statistically significant, patients with adenocarcinoma appeared to derive the least benefit from chemoimmunotherapy. Given that squamous cell carcinoma is known to be associated with male sex and smoking, tumors with this histology may be more likely to be more immunogenic and responsive to immune system enhancing therapies. The extent to which other histologies derive benefit from immunotherapy warrants further examination. A recent study by Tuminello *et al.* [2022] analyzed population-level from the national cancer database (NCDB) and found males with squamous cell carcinoma may derive more benefit from chemoimmunotherapy than females (38); in turn, they hypothesized that histology likely plays an important role in the modulation of sex on immunotherapy effectiveness (38).

Notably, the lack of significant association of OS with either race or Charlson Comorbidity status should not preclude future research and analyses of these characteristics with larger patient samples. In general, better reporting of outcomes by race is necessary, especially given preliminary evidence of differential tumor mutations patterns that may lend themselves to different targeted treatment plans. Black patients are 13% of the US population, but in the SEER chemoimmunotherapy and chemotherapy treatment groups presented here, only 6.3% (n=22) and 8.3% (n=93) of patients respectively were Black. This suggests analyses for race are likely underpowered and that there may be underlying disparities in accessing specialty cancer care, impacting patient outcomes. Calculations concerning comorbidity status were also likely to be underpowered as only 39 and 34 patients had a Charlson score of 2 or ≥3 respectively. Nevertheless, race and comorbidity status should not be ruled out as pertinent factors that could potentially contribute to heterogeneity in immunotherapy response rates as future research can re-examine these characteristics with larger patient cohorts and extended follow-up windows for survival (39).

Strengths and limitations

To our knowledge, this is the first study to analyze the SEER-Medicare dataset and use specifically defined immunotherapy agents in evaluating how multiple personal and clinical characteristics moderate the effectiveness of immunotherapy. These findings are more generalizable to real world experiences than clinical trials or single site studies which disproportionately over-enroll younger, male, and healthier patients. Moreover, reporting of interaction terms allows for a formal assessment of differences in the effectiveness of immunotherapy by strata. Furthermore, compared to other registry data sources, like the NCDB which often define "immunotherapy" broadly to cover a large array of administered agents, SEER-Medicare allowed for more specificity in selecting particular agents—pembrolizumab, nivolumab, and atezolizumab, due to its use of billing codes. The detailed clinical data available in the SEER-Medicare dataset is another strength and enables adjustment for unique patient-level characteristics

(e.g., marital status and comorbidities) that may otherwise confound analyses in clinical trials and meta-analyses.

Results should be interpreted within the context of this study's limitations. First, SEER-Medicare does not report on smoking-status, genetic markers, or tumor mutation burden. Therefore, there is a limit to the extent to which these findings can be interpreted and future research on these factors is warranted, especially because there are likely to be sex-based differences, and the degree of difference and how it pertains to chemoimmunotherapy benefit is unclear.

Additionally, SEER-Medicare does not record information about disease progression, and it is not possible to determine from the dataset the order in which chemotherapy and immunotherapy were administered. Therefore, it is possible that some patients received immunotherapy because their disease had progressed, causing us to underestimate the effectiveness of immunotherapy. However, we focused our analysis on stage IV diagnosed patients, where surgery and radiation are not indicated, to limit this possibility. The sensitivity analysis on a smaller sample size where information on brain metastasis at diagnosis was available corroborates our primary findings, as this allowed us to adjust more comprehensively for covariates associated with survival and treatment response, and it still corroborated our primary findings. As this analysis was limited to patients >65 years, we were unable to explore the effect of immunotherapy in younger patients, but as the median age of diagnosis for NSCLC is 70 years, we believe the effect of excluding these patients is small (40). As approval and use of pembrolizumab, nivolumab, and atezolizumab is recent, years of available data and follow up were limited. As more data becomes available, and more patients are treated with these agents, these questions should be further explored.

Conclusions

The findings from our national SEER-Medicare patient sample suggest chemoimmunotherapy is associated with better OS compared to chemotherapy alone, but that males may derive more benefit than females. Therefore, sex may be a useful predictor of chemoimmunotherapy effectiveness. There is limited evidence suggesting age, histology, race, and comorbidity status contribute to differences in chemoimmunotherapy effectiveness and subsequent survival disparities. Future research ought to explore underlying mechanisms between sex and chemoimmunotherapy response and re-examine other personal characteristics as more patients are treated and more data becomes available. In turn, clinicians will be better positioned to uniquely tailor chemoimmunotherapy treatment strategies to patients with distinct clinical profiles.

Acknowledgments

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; the Office of Research, Development and Information, Center for Medicare Services (CMS); Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Funding: This work was supported in part by the National Cancer Institute (No. P30CA196521) and KHP received a student stipend from the Tisch Cancer Institute as part of the Icahn School of Medicine's summer cancer fellowship. ST is supported by a National Research Services Awards T32 award from the Health Resources and Services Administration and the Agency for Healthcare Research and Quality.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-682/rc

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-682/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-682/coif). KHP received $5,500 stipend as part of the Tisch Cancer Institute (TCI) Summer Scholars Program for Icahn School of Medicine's cancer fellowship to cover living expenses. Funding did not go towards anything other than living expenses. ST is supported by a National Research Services Awards T32 award from the Health Resources and Services Administration and the Agency for Healthcare Research and Quality. National Cancer Institute (NCI) grant P30CA196521 awarded to ET at the Icahn School of Medicine at Mount Sinai. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of the Mount Sinai School of Medicine, in accordance with Mount Sinai's Federal Wide Assurances (FWA#00005656, FWA#00005651) and a waiver of informed consent was obtained for all patients as part of the IRB application.

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Cite this article as: Patel KH, Alpert N, Tuminello S, Taioli E. Personal and clinical characteristics associated with immunotherapy effectiveness in stage IV non-small cell lung cancer. Transl Lung Cancer Res 2023;12(6):1210-1220. doi: 10.21037/tlcr-22-682

Supplementary

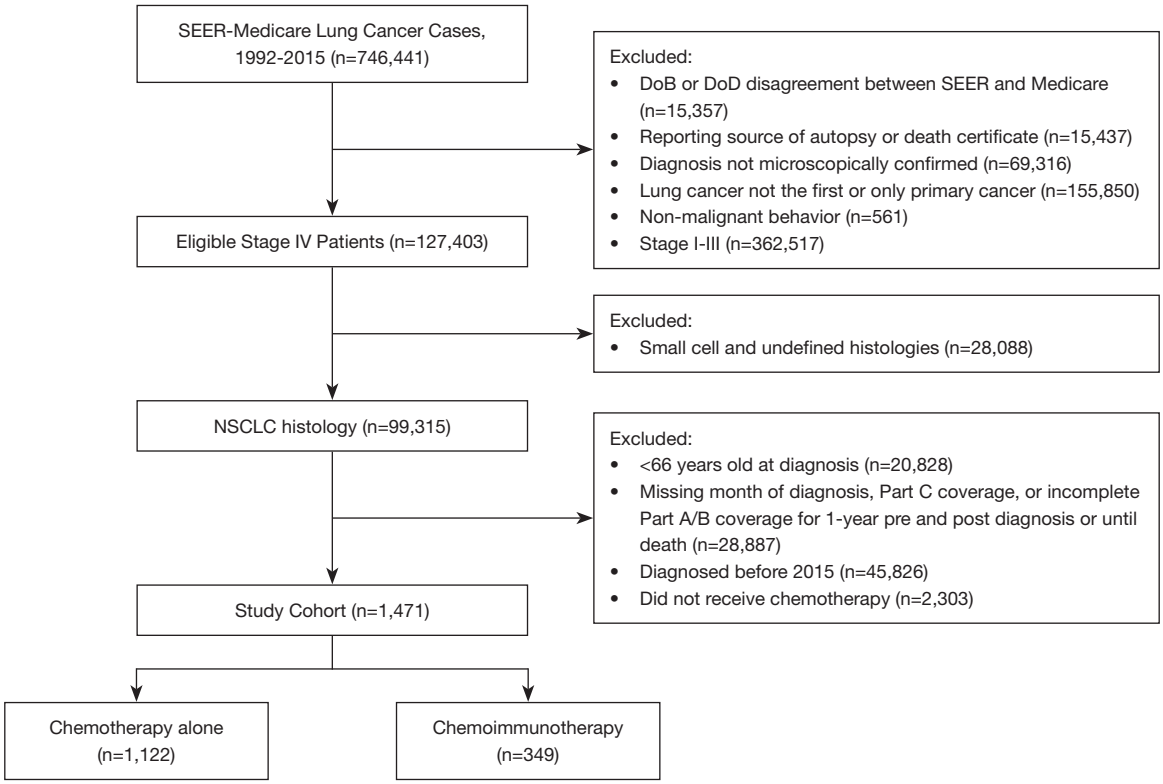

Figure S1 SEER-Medicare cohort selection. SEER, Surveillance, Epidemiology, and End Results; DoB, date of birth; DoD, date of death; NSCLC, non-small cell lung cancer.

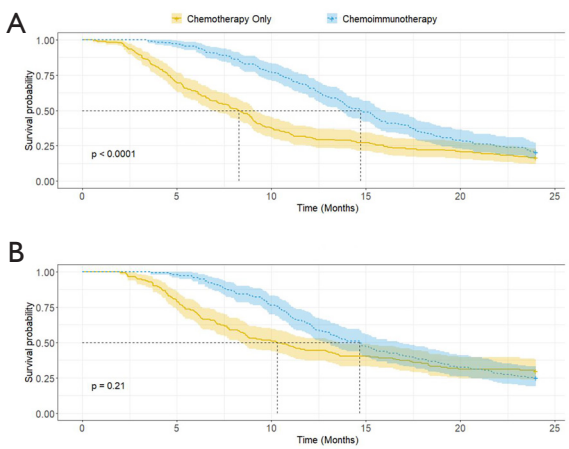

Figure S2 Overall survival according to treatment in the stratified propensity matched cohort for (A) males (n=360) and (B) females (n=302).

https://dx.doi.org/10.21037/tlcr-22-682

Table S1 HCPCS codes used to identify chemotherapy and immunotherapy in Medicare claims (41)

Agent	HCPCS
Immunotherapy	
Pembrolizumab	C9027; J9271
Nivolumab	C9453; J9299
Atezolizumab	C9483
Chemotherapy	
Cisplatin	C9418; J9060; J9062; J9045
Carboplatin	J9045
Paclitaxel (Taxol); albumin-bound paclitaxel (nab-paclitaxel, abraxane)	C9127; C9431; J9264; J9265; J9267
Docetaxel (Taxotere)	J9170; J9171
Gemcitabine (Gemzar)	J9201
Vinorelbine (Navelbine)	C9440; J9390
Etoposide (VP-16)	C9414; C9425; J8560; J9181; J9182
Pemetrexed (Alimta)	C9213; J9305

HCPCS, Healthcare Procedural Coding System.

Table S2 Propensity matched analysis of the association of chemoimmunotherapy with survival according to sex and histology

Propensity-matched strata (n=662)	HR_{adj} (95% CI), chemoimmunotherapy *vs.* chemotherapy alone	P value (strata*receipt of chemoimmunotherapy interaction)
Sex		0.0414
Male (n=360, 180 matched pairs)	0.59 (0.47–0.74)	
Female (n=302, 151 matched pairs)	0.85 (0.65–1.12)	
Histology		0.1655
Squamous (n=188, 4 matched pairs)	0.71 (0.54–0.95)	
Adenocarcinoma (n=394, 197 matched pairs)	0.91 (0.73–1.15)	
Other (n=80, 40 matched pairs)	0.52 (0.31–0.88)	

Propensity matched (per procedures described under methods) and adjusted for age, sex, race, marital status, CCI, and histology. Sex and histology specifically selected given presence of statistically significant findings within non-propensity matched patient subsets. CCI, Charlson Comorbidity Index.

https://dx.doi.org/10.21037/tlcr-22-682

Table S3 Sensitivity analysis of factors independently associated with mortality, adjusting for presence of metastasis to brain at diagnosis

Variables	HR_{adj} (95% CI), n=1,402[†]
Chemoimmunotherapy *vs.* chemotherapy alone	0.72 (0.63–0.83)
Age at diagnosis, years	
66–69	1.0 (ref)
70–74	1.03 (0.88–1.21)
75–79	1.08 (0.91–1.27)
≥80	1.28 (1.07–1.54)
Sex (female *vs.* male)	0.73 (0.64–0.83)
Race	
White	1.0 (ref)
Black	0.80 (0.63–1.00)
Other	0.81 (0.60–1.09)
Marital status (married *vs.* unmarried)	0.91 (0.79–1.03)
Charlson Comorbidity Index	
0	1.0 (ref)
1	1.02 (0.88–1.18)
2	1.00 (0.84–1.20)
≥3	1.21 (1.01–1.46)
Histology	
Squamous	1.0 (ref)
Adenocarcinoma	0.89 (0.77–1.02)
Other	1.34 (1.10–1.63)
Metastasis to brain at diagnosis (yes *vs.* no)	1.41 (1.22–1.63)

[†], adjusted for age, sex, race, marital status, Charlson Comorbidity status, histology (all of the above variables), 49 patients excluded because marital status missing/unknown, 20 patients excluded because brain metastasis status unknown. Bolded results indicated statistical significance.

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