Racial Disparities in Survival Among Advanced Non-Small Cell Lung Cancer Patients First-Treated with The Combination of Paclitaxel and Platinum

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Research

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Racial Disparities in Survival Among Advanced Non-Small Cell Lung Cancer Patients First-Treated with The Combination of Paclitaxel and Platinum

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Abstract

Background: In clinical practice, different chemotherapy schedules for NSCLC have potential impacts on overall survival, but not specific in NCCN guidelines. Although some meta-analyses have been conducted to identify the influencing factors, the results are limited by method. Our study is helpful to supplement the NCCN Guidelines.

Methods: In order to evaluate and quantify the potential relationship between demographic characteristics, disease characteristics, etc. and overall survival as well as their impact on objective response rate and safety, we developed parametric proportional hazard regression models to describe the overall survival of advanced NSCLC patients first-treated with the paclitaxel-platinum regimen.

Results: The principal finding of this research was that race significantly affected hazard of dying. Hazard of dying was 1.4 times higher in non-East Asians than in East Asians, and the hazard ratio of the OS curve was 0.71(95%CI: 0.65-0.78). The median survival time in East Asians and non-East Asians were estimated as 12.2 (95%CI: 10.5, 14.4) and 8.4 (95%CI: 6.5. 11.0) months, respectively. The ORR was 37% (95%CI: 32, 41) and 28% (95%CI: 25, 32) in East Asians and non-East Asians, respectively.

Conclusions: Paclitaxel-platinum regimen had different efficacy in two racial groups. The developed model suggests that the efficacy and safety of paclitaxel-platinum regimen can vary between different racial populations because of differences in influencing factors (doses, platinum type, cycles, etc.)

Keywords: Paclitaxel, Platinum, Advanced NSCLC, Overall Survival, Modeling and

simulation

1. Background

Over the past decade, targeted therapy and immunotherapy have led to new developments in the treatment of non-small cell lung cancer (NSCLC) based on molecular and immunological research.[1] Research in this area has shown that the incidence of NSCLC with EGFR mutation is the highest among various molecular subtypes. Approximately 20% of patients with advanced NSCLC have EGFR mutation, with ALK rearrangement, MET mutation, ROS1 rearrangement, and BRAF mutation showing a prevalence of approximately 5%, 4%, 1%, and 2%, respectively.[2] However, more than 50% of patients with advanced NSCLC still have unknown gene mutations, and thus cannot receive targeted therapy.[3] Lee (2014) compared targeted therapy and conventional chemotherapy in EGFR wild-type patients, and the results showed that conventional chemotherapy led to significantly higher progression-free survival (PFS) and objective response rate (ORR) than targeted therapy.[4] In immunotherapy, patients with PD-L1 expression levels above 50% could significantly benefit from conventional chemotherapy; however, in fact, only 23-28% of patients with advanced NSCLC had high PD-L1 expression levels.[5] Therefore, most patients cannot benefit from targeted therapy or immunotherapy, and chemotherapy remains the cornerstone of treatment for advanced NSCLC.

The combination of paclitaxel and platinum drugs is a recognized first-line chemotherapy regimen for the treatment of advanced NSCLC.[6] However, the NCCN

Clinical Practice Guidelines in Oncology for NSCLC recommend conventional treatment options without clarifying the specific details, such as the times of administration, cycles of chemotherapy, and doses of paclitaxel in combination with platinum drugs, and thus may cause great differences between different paclitaxel-platinum regimens in clinical practice. Of particular concern is that the efficacy and safety of a paclitaxel-platinum regimen may not be identical in different populations. In a study by Soo (2011), Asians and Caucasians showed different responses to chemotherapy; Asians, who also received chemotherapy for advanced NSCLC, showed higher overall survival (OS) rates and longer median survival time than Caucasians.[7] Consequently, finding a safer and more effective chemotherapy regimen for a paclitaxel-platinum regimen in different populations is not only beneficial for clinical practice but also a great help for the development of new drugs. In many clinical trials of new drugs, a paclitaxel-platinum regimen is often used as a positive control, basic therapy, and even external control for single-arm trials. Heterogeneity of treatment plans and patient populations in different trials may lead to differences in efficacy and safety. Therefore, when evaluating the sample size of new drugs in clinical trials, or when determining the cutoff value of efficacy or safety in external controls, caution should be taken to find the relevant literature data.

Gao (2012) found that paclitaxel had similar efficacy but better safety when administered once a week versus every 3 weeks, and the weekly schedule was suitable for elderly patients who could not tolerate the standard regimen and for patients with poor performance status scores.[8] In terms of chemotherapy cycles, Soon (2009) found

that longer cycles can statistically increase OS and PFS, but did not investigate whether the extension of the cycle would increase the incidence of adverse events.[9] Moreover, this study was published relatively early, and only a few trials were included; thus, there are some potential limitations. Thus far, several studies have indicated that six cycles and three to four cycles of platinum-based first-line treatment did not significantly improve OS and PFS in patients with advanced NSCLC. In addition, the incidence of anemia was higher with six cycles; thus, fewer cycles of chemotherapy were recommended.[10] It should be noted that these studies did not distinguish the heterogeneity of subjects in the trial, and thus their conclusions may be more prone to bias.

Model-based meta-analysis (MBMA) is a powerful analytical method for dealing with heterogeneity. Quantitative analysis of influencing factors can be conducted simultaneously by establishing a covariate model and obtaining quantitative results by evaluating the degree of influence of those factors on efficacy or safety. Importantly, MBMA can be used to analyze OS rate in the entire time course and not just in a single index, such as median survival time and 1-year survival rate, by establishing a proportional hazard regression model. After a hazard model is developed, it can be used to predict OS rate at any time within 5 years, such as 0.5, 1, 1.5, and 2 years, showing better flexibility and practicability in the evaluation of new drugs.

In this study, MBMA was conducted to explore and quantitatively assess the influencing factors of paclitaxel-platinum regimens as a first-line chemotherapy in patients with advanced NSCLC, including cycles of chemotherapy, dosage, times of

106 administration, and baseline characteristics of patients. We hope this research will offer
107 a fresh perspective on the quantitative information necessary for clinical practice and
108 provide a more accurate cutoff value for the distribution of positive drugs for clinical
109 trials of new drugs.
110

111 # 2. Patients and Methods

112 ## 2.1 Literature sources

113 A systematic literature search was performed using PubMed and the Cochrane
114 Library and completed on July 1, 2019. The terms “carboplatin,” “cisplatin,”
115 “paclitaxel,” “albumin-bound paclitaxel,” and “non-small cell lung cancer” were the
116 key words used in the search. The search was limited to English language literature and
117 clinical trials. Specific details on the search strategy are shown in the Supplementary.
118

119 ## 2.2 Patients, data extraction, and software

120 All patients had advanced stage IIIB and IIIC or stage IV NSCLC and received
121 carboplatin/cisplatin in combination with paclitaxel/albumin-bound paclitaxel as a first-
122 line chemotherapy regimen. The patients had not received any treatment before
123 enrollment, including surgical resection, radiotherapy, or chemotherapy. Specific
124 inclusion and exclusion criteria are detailed in the Supplementary.
125 Excel (Microsoft, USA) was used to manage the literature characteristics, trial
126 design, demographic characteristics, disease characteristics, efficacy, and safety results.
127 The Engauge Digitizer (Mark Mitchell, USA) software was used to extract survival data

from Kaplan-Meier curves in the literature.

NONMEM7.3 (ICON Development Solutions, USA) was used to construct the model and Bayesian feedback of model parameters in each experimental group. Model simulation and graph drawing were completed by R4.0.1 (Lucent Technologies, USA). Meta-analysis was performed using Stata Software Version 14 (2013; Stata Corp LP, College Station, TX, USA). $P \leqslant 0.05$ indicated a statistically significant difference.

2.3 Literature quality evaluation

The Cochrane Risk of Bias Table was used to evaluate literature quality, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Other biases were defined as baseline characteristics that were not comparable between different groups in the trial.

2.4 Modeling analysis of overall survival

2.4.1 Model development and model selection criteria

In this study, a parametric proportional hazard regression model was used to explore OS data so as to analyze the distribution of OS time of patients treated with a paclitaxel-platinum regimen. The hazard function for death was based on the following equation:

Hazard function $$h(t) = h_0(t) \cdot e^{(\alpha_1 \cdot x_1 + \alpha_2 \cdot x_2 + \cdots + \alpha_n \cdot x_n + \eta)} \quad (1)$$

Exponential function $$h_0(t) = \lambda_0 \quad (2)$$

Gompertz function $$h_0(t) = \lambda_1 \cdot \exp(\beta_1 \cdot t) \quad (3)$$

Weibull function $$h_0(t) = \lambda_1 \cdot \exp(\beta_1 \cdot \ln(t)) \quad (4)$$

Cumulative hazard function $$\Lambda(0,\ t) = \int_0^t h(t)\, dt \quad (5)$$

Survival function $$\mathrm{S}(t)_i = \exp(\ -\ \int_0^t h(t)_i dt)\ + w_{i,t} \cdot \varepsilon_{i,t} \quad (6)$$

Standard error function $$\mathrm{SE}_{i,\,t} = \sqrt{\frac{P_{i,\,t} \times (1 - P_{i,\,t})}{N_{i,\,t}}} \quad (7)$$

OS rate is affected by many factors in survival analysis, and censored data are included in many studies. The distribution of OS was not exactly determined nor did it meet the normal distribution and homogeneity of variance. Therefore, hazard rate was used as a dependent variable in this study.

In formula (1), h(t) represents the instantaneous hazard of dying at time t, which was obtained by multiplying two parts. Among them, $h_0(t)$ describes the base hazard function, in which instantaneous hazard of dying changed over time. We first examined the fitting effectiveness of the exponential, Gompertz, and Weibull functions on survival data. In formulas (2)-(4), λ_0 and λ_1 represent the hazard rate at time 0, and β_1 represents the regression coefficient of the hazard rate changing over time. In the exponential function, hazard rates were assumed to be constant values that did not change over time. Therefore, hazard rates were constant at each moment. However, in the Gompertz and Weibull functions, hazard rates would change over time as a function of exponential. $e^{(\alpha_1 \cdot x_1 + \alpha_2 \cdot x_2 + \cdots + \alpha_n \cdot x_n + \eta)}$ describe the effect of covariates on hazard rates, where x_1, x_2, ..., x_n represent 1-n covariates that affect hazard rates, and their impact coefficients on hazard rates are α_1, α_2, …, α_n. In formula (5), Λ (0, t) is the

cumulative hazard rate from time 0 to t, which is the integral value of the hazard function h(t) from time 0 to t. In formula (6), $S(t)_i$ is the survival function at time point t for the i-th study, which was the reciprocal of the exponential cumulative hazard of dying ($e^{-\Lambda(0,t)}$). When $S(t)_i$ is 0.5, t is the median survival time of the i-th study. $\varepsilon_{i,t}$ is the residual variation in survival rate at time t in the i-th study, and needs to be corrected by the standard error of the survival rate ($SE_{i,t}$) at that time point. That is, the larger the standard error, the greater the residual variation.

After establishing the base model, a covariate model was developed using the forward inclusion-backward elimination method. We screened out covariates that affected hazard of dying, including age, gender, performance status, clinical stage, pathological type, dosage, platinum type (carboplatin or cisplatin), cycles of chemotherapy, times of administration, and race. If the above covariates were not available in some studies, the median was used. As hazard of dying was the parameter, the inclusion and elimination procedures of all covariates were carried out on λ. The boundary values of forward inclusion and backward elimination were set to $P<0.05$ and $P<0.01$, respectively. Continuous variables were introduced as formula (8), and categorical variables were introduced as formula (9):

$$\lambda_{0_{individual}} = \lambda_{0_{typical}} \times e^{(\eta+(COV-COV_{median})\times\theta_{COV})} \quad (8)$$

$$\lambda_{0_{individual}} = \lambda_{0_{typical}} \times e^{(\eta+COV\times\theta_{COV})} \quad (9)$$

In the covariate screening, the influence of a single covariate on the efficacy end point (OS) was investigated for primary screening. The detailed process is shown in Supplementary Table 1. If the objective function value of the model decreased by more

than 3.84 (df=1, P=0.05), the covariate was considered to have a significant influence on the parameters. Next, previously selected covariates were introduced forward and eliminated backward one by one to identify the covariates that had a significant influence on the model.

$\lambda_{0individual}$ is the parameter value for hazard of dying in each study, and $\lambda_{0typical}$ is the typical value for hazard of dying in each study. COV is the covariate value of each study, COV_{median} is the median value of the covariate, and θ_{COV} is the correction factor of the covariate to hazard rates. η is the inter-trial variation of hazard rates. That is, the variation could not be explained by covariates.

2.4.2 Model evaluation

After the final model was established, the goodness-of-fit of the model was visually evaluated using the R (Lucent Technologies, USA) software, in which predicted values and residuals were checked to assess the potential bias of the model. Next, sampling of the final model parameters was repeated 1000 times by Bootstrap to obtain the median and 95% confidence interval (95%CI) of the model parameter distribution. They were then compared with the final model parameters to evaluate the stability of the model. Finally, we conducted 1000 simulations of the final model using the Monte Carlo method to obtain the median OS at each time and the 95%CI. Comparison of intervals with observations as well as visualization of the results were performed using the R software to determine whether the model is reliable and can accurately predict the results.

2.4.3 Simulation

After the final model was constructed, we found that some covariates significantly influenced OS in the screening process. The typical survival time curve and 95%CI of the covariate at different levels could be simulated based on the final model parameters. We calculated the median survival time and survival rates within 5 years.

This study focused on the covariates (paclitaxel doses, platinum type, cycles of chemotherapy, and times of administration) related to the regimen. Even if the above factors were not found to significantly affect OS, the OS distribution of these covariates for different levels would be obtained through the following methods. The specific method was to obtain the model parameters of each experimental group using Bayesian feedback. Subsequently, to obtain the distribution of efficacy parameters at different covariate levels, the random-effects model in the single-arm meta-analysis was used to combine and analyze the model parameters of each group according to the different covariate levels. That is, the point estimates of the model parameters and their 95%CIs. The parameters were then randomly drawn from the model distribution at each covariate level, and the survival rate at each time point was calculated. This process was repeated 1000 times to obtain the typical value of the survival time curve and their 95%CIs at different covariate levels. Finally, we calculated the median survival time and survival rates within 5 years.

2.5 Objective response rate and safety analysis

The random-effects model in the single-arm meta-analysis was used to analyze ORR and the incidence of grade 3-4 adverse effects (AEs) in each experimental group

according to the different covariate levels to obtain the typical values of ORR and the incidence of AEs at different covariate levels. Their 95%CIs were also obtained.

3. Results

3.1 Data Characteristics

In total, 31 articles were included.[11-41] A total of 3,365 participants from 37 experimental groups were included in the analysis. The flow chart of the literature screening is shown in Figure 1. The baseline characteristics of the patients are shown in Table 1. The participants were all previously untreated patients with advanced or metastatic NSCLC who received a paclitaxel-platinum regimen as a first-line chemotherapy. Drugs were administered intravenously. The median age of these patients was 62.5 years (range 26–87 years), and most of them presented with advanced clinical stage IV (20.4% stage IIIB and 79.6% stage IV). Most patients (98.3%) had an ECOG PS of 0-1. Regarding histology, squamous cell carcinoma accounted for 29% of cases, and adenocarcinoma accounted for 50%. The proportions of other histology, such as large cell carcinoma and adenosquamous carcinoma, were minor. A total of 13.7% of the patients were from East Asia (including China, Japan, and South Korea).

The median administered dose of paclitaxel was 175 mg/m^2(range 40–225 mg/m^2). The median administered dose of carboplatin was AUC = 6 mg/mL· min (range AUC = 2–6 mg/mL· min). The median administered dose of cisplatin was 75 mg/m^2 (range 20–200 mg/m^2). In terms of chemotherapy cycles, 75.1% of patients received 4-6 cycles, 57.4% received 6 cycles, and 15.9% received 4 cycles, with 21-day and 28-day cycles

accounting for 88.4% and 2.7%, respectively. Regarding the times of drug administration, 77.1%, 3%, and 3.7% of patients were administered paclitaxel once, twice, and three times, respectively, and 76.6%, 3%, and 4.2% of patients were administered platinum drugs once, twice, and three times, respectively. Regarding dosage forms, albumin-bound paclitaxel and paclitaxel liposomes were used in only two trials, and paclitaxel was in used the remaining trials. Among platinum drugs, cisplatin liposomes were used in only one trial, and cisplatin or carboplatin was used in the remaining trials.

3.2 Model development and evaluation

3.2.1 Overall survival

Analysis of pooled data from the 31 included trials revealed that the exponential hazard function had the best description of OS among the hazard function models, as it showed the most stable estimation of model parameters. Therefore, the exponential hazard function was chosen as the base hazard model. During covariate screening, we found that race had a significant influence on hazard of dying. The hazard of dying in non-East Asians was 1.4 times ($e^{0.37}$) higher than that in East Asians. The estimated values of the parameters of the final model are shown in Supplementary Table S5, and the covariate model is expressed as follows:

$$h(t) = 0.0572 \cdot e^{(Race \cdot 0.37)} \qquad (10)$$

In formula (10), Race 0 represents East Asians, and Race 1 represents non-East Asians. That is, the typical instantaneous hazard of dying in East Asians was 0.0572,

and that in non-East Asians was 0.08281 ($0.0572 \cdot e^{0.37}$). The final model is as follows:

$$P_i = e^{-\int_0^{t_j}(0.0572 \times e^{(N(0,0.245^2)+RACE \times 0.37)})} + \sqrt{\frac{P_{i,j}(1-P_{i,j})}{N_{i,j}}} \times (N(0, 1.916^2)) \quad (11)$$

P_i is the OS probability of the i-th experimental group. N (0, 0.245^2) is the intergroup variation, which satisfied the normal distribution of mean 0 and standard deviation 0.245. N (0, 1.916^2) is the intragroup variation, which satisfied the normal distribution of mean 0 and standard deviation 1.916.

After the final model was established, parameter values and standard errors were estimated by Bayesian feedback. Bootstrap was successfully minimized 1,000 times. The median of the model parameters estimated by Bootstrap and its 95%CI were very close to the estimated parameters of the final model. This further indicates the robustness of our model. The model diagnostic plots are displayed in Supplementary Figure S2, which shows that the population predicted values versus observed values were relatively uniformly distributed around 0. Although there were some dispersions compared with the individual predicted values, considering that the population predicted values contained intergroup variations, conditional weighted residuals were distributed between ± 4. In the plot of time versus conditional weighted residuals, distribution was slightly uneven, which may be related to the different visit times of each experimental group. These trials mainly focused on the visit point within 16 months. The VPC plot generated using the Monte Carlo method, as shown in Supplementary Figure S4, showed that most of the observed values fell within the 95%CI of the predicted values. The results indicated the good predictive ability of the

297 model. In summary, the model could accurately predict the OS probability of patients
298 at each visit point.

299 The simulated results are shown in Figure 2, where the typical OS curve of East
300 Asians was significantly different from that of non-East Asians. The 95%CIs of the
301 respective typical OS curves did not overlap (hazard ratio, 0.71;95% CI, 0.65 to 0.78).
302 It was estimated that the median survival time in East Asians and non-East Asians was
303 12.2 (95%CI: 10.5, 14.4) and 8.4 (95%CI: 6.5. 11.0) months, respectively. As shown in
304 Table 2, 1-year OS rates in East Asians and non-East Asians were 50.3% (95%CI: 45.0,
305 56.1) and 37.2% (95%CI: 27.3. 46.2), respectively. The estimated OS rates at other
306 times are shown in Table 3.

307 Among the covariates predicted to be related to the regimen, none was found to
308 have a significant effect on OS in the final model; however, OS curve for different
309 schedules could still be obtained according to the distribution of model parameters
310 under different schedules. As race had a significant effect on OS, to avoid the effect of
311 heterogeneity on the results, we conducted a subgroup analysis based on race. Because
312 of the complexity of race, all patients were divided into two major groups according to
313 region: East Asians and non-East Asians. We explored the effects of four cycles of
314 chemotherapy versus six cycles; 21 days per cycle versus 28 days; platinum drugs
315 administered 1, 2, or 3 times per cycle; paclitaxel administered 1, 2, or 3 times per cycle;
316 paclitaxel doses; and carboplatin versus cisplatin on OS in the two racial groups. The
317 results of this analysis are presented in Figure 2. In Non-East Asians, six cycles of
318 chemotherapy versus four cycles; 21 days per cycle versus 28 days; paclitaxel 200–225

319 mg/m^2 versus 175 mg/m^2; and paclitaxel administered once per cycle versus three times
320 significantly increased OS time. OS was significantly longer with 21 days per cycle
321 than with 28 days per cycle. One-time paclitaxel administration per cycle led to
322 significantly longer OS than three-time paclitaxel administration per cycle. The same
323 trends were observed in East Asians. However, the trends were not obvious owing to
324 the small sample size of the experimental groups and the large variation between trials.
325 In addition, one interesting result emerged that carboplatin tended to be more effective
326 than cisplatin in East Asians, but showed no obvious tendency in non-East Asians.
327
328 **3.2.2 Objective response rate**
329 Meta-analysis of ORR between the two racial groups showed that ORR in East
330 Asians was significantly higher than that in non-East Asian patients, which manifested
331 as not overlapping 95%CIs. According to the meta-analysis, the ORR was 37% (95%CI:
332 32, 41) and 28% (95%CI: 25, 32) in East Asians and non-East Asians, respectively.
333 However, as shown in Figure 3A-B, there was no significant difference in ORR between
334 East Asians and non-East Asians at different covariate levels in the subgroup meta-
335 analysis of ORR.
336
337 **3.2.3 Adverse effects**
338 The meta-analysis results of grade 3-4 AEs in the two racial groups are shown in
339 Supplementary Table S6. In hematological toxicity analysis, there was a significant
340 difference between the two racial groups in the incidences of leukopenia, neutropenia,

and febrile neutropenia. The incidences of these AEs in East Asians and non-East Asians were 27% (95% CI: 17, 37) and 11% (95% CI: 8, 15), 54% (95% CI: 41, 67) and 19% (95% CI: 14, 25), and 20% (95% CI: 6, 51) and 3% (95% CI: 1, 6), respectively. Among non-hematological toxicities, only nervous system disease was significantly different between the two racial groups; its incidence was 3% (95%CI: 1, 5) in East Asians and 9% (95%CI: 6, 13) in non-East Asians. Figure 3C-F presents the meta-analysis results of grade 3-4 AEs in the subgroups. There were significant differences in the incidence of AEs between the two racial groups at different covariate levels. In both racial groups, the incidence of leukopenia was significantly higher following six cycles of chemotherapy than after four cycles of chemotherapy. Moreover, the incidence of leukopenia with 28 days per cycle was higher than that with 21 days per cycle in non-East Asians. The incidence of neutropenia following one-time paclitaxel administration per cycle was higher than that after three-time administration. Neutropenia incidence was also different between 28 days per cycle and 21 days per cycle. In East Asians, there were differences in the incidence of leucopenia between cycles of chemotherapy and between platinum types.

4. Discussion

In reviewing the literature, little data were found on the association between OS and the different influencing factors (doses, platinum type, cycles of chemotherapy, times of administration). One of the aims of this study was to simulate the relationship between OS and different influencing factors in the two racial groups (East Asians and

non-East Asians) treated with a paclitaxel-platinum-based regimen, as well as the relationship between ORR, grade 3/4 AEs, and these influencing factors. The most obvious finding of the analysis was that the efficacy end point (OS) in non-East Asian patients was related to cycles of chemotherapy, duration (days) of one cycle, doses, and times of paclitaxel administration. The efficacy end point (OS) was related to platinum type in East Asians. Another important finding was that the incidence of leukopenia was related to cycles of chemotherapy and duration (days) of one cycle, and that neutropenia was related to the times of paclitaxel administration and duration (days) of one cycle in non-East Asian patients. The incidence of leukopenia in East Asian patients was related to cycles of chemotherapy and platinum type.

Our results showed that non-East Asians achieved longer OS when administered paclitaxel 200–225 mg/m^2 once every 3 weeks for six cycles of chemotherapy. In contrast, the incidence of leukopenia was significantly higher with six cycles than with four cycles of chemotherapy. And the incidence of leukopenia was significantly higher with 28 days per cycle than with 21 days per cycle. The incidence of neutropenia was significantly higher when paclitaxel was administered once compared with when it was administered three times. Meanwhile, there were considerable differences in the incidence of neutropenia between 21 days per cycle and 28 days per cycle. This may occur because, owing to the lack of data on neutropenia, the confidence intervals were not completely separated and the difference was not significant. Sakakibara (2009) and Belani (2008)[42, 43] reported that all efficacy parameters were similar between weekly and the standard every-3-week administration of carboplatin combined with paclitaxel.

Their results were in accordance with our current findings, indicating that three-time paclitaxel administration was less toxic than but had comparable efficacy to one-time administration. This intriguing result could be attributed to the nonlinear pharmacokinetic behavior of paclitaxel. Paclitaxel systemic exposure is significantly increased as its systemic clearance is decreased, which changes its pharmacodynamics and increases the risk of systemic toxicity.[44, 45] Longer infusion of paclitaxel caused greater myelosuppression, but did not lead to higher response rate.[46] In our study, as no data on infusion time were collected, it was impossible to verify whether infusion time affects the incidence of AEs. However, previous studies showed that there was no difference in OS between different infusion times.

In East Asians, carboplatin was more effective than cisplatin, but led to higher incidence of leukopenia. On the contrary, in a study by de Castria (2013)[47], there was no significant difference in OS between cisplatin and carboplatin. It is possible that this previous finding was due to the lack of distinction between racial groups. In addition, our analysis revealed that four cycles of chemotherapy had better safety and lower incidence of leukopenia than six cycles of chemotherapy.

In the meta-analysis of ORR and the incidence of grade 3-4 AEs, meta-regression was used to explore the source of heterogeneity to avoid its influence. Further analysis showed that race, platinum type, and paclitaxel dose were the sources of heterogeneity in ORR, but there was no correlation between these factors. Race was the source of heterogeneity in the incidence of leucopenia and neutropenia. We then performed a subgroup analysis of ORR, leukopenia incidence, and neutropenia incidence in two

racial groups. The results showed that the heterogeneity was significantly reduced, but still present. Further meta-regression revealed that platinum type was the source of heterogeneity in ORR among non-East Asian patients, and cycles of chemotherapy were the source of heterogeneity in leucopenia incidence. In addition, platinum type was the source of heterogeneity in leucopenia incidence among East Asians. The sources of heterogeneity, as identified by meta-regression, were consistent with the results of the meta-analysis. However, as meta-regression could not fully explain all heterogeneity, residual heterogeneity was still present.

Our analysis was based on the data provided by authors of the pooled studies, not on individual patient data. Despite our novel findings, there were several limitations to our study. First of all, because some studies did not indicate the race of patients, this study mainly divided two racial groups by region (East Asians and non-East Asians). In the sensitivity analysis, we found that after the data of Indians were deleted, the change rate of model parameter estimates was only 0.2%. The results indicated that the stability of the model was not affected by it, and that these two racial groups could be considered equivalent to western and Asian populations. Second, considering that the efficacy of paclitaxel may be affected by the dosage forms, a related sensitivity analysis was also conducted in this study. Socinski (2012) and Tan (2018) noted that solvent paclitaxel and albumin-bound paclitaxel in combination with carboplatin prolonged OS in an elderly group, but the young group also showed similar results[48, 49]. Our results indicated that after the data on albumin-bound paclitaxel and liposomal paclitaxel were deleted, the rate of change of model parameter estimates was 4%, which was less than

5%. Next, by comparing 95%CI between the simulated efficacy and the original model, we found a high coincidence of these intervals. The most important result was that after the data on Indians, albumin-bound paclitaxel, and liposomal paclitaxel were deleted, race remained as the covariate that significantly affected OS. Our analysis confirms that compared with non-East Asians, East Asians had a better efficacy with paclitaxel-platinum regimen. We believe that the findings of this study will help most patients in NSCLC and be helpful to supplement the NCCN Guidelines. At the same time, we suggest that later studies should focus on the differences in efficacy between races.

5. Conclusion

This study aimed to develop a model for quantitative analysis of the effects of different covariates on the OS of previously untreated advanced NSCLC patients treated with a paclitaxel-platinum-based regimen. The results showed that the paclitaxel-platinum-based regimen had different efficacy in two racial groups, namely Non-East Asians and East Asians. Therefore, this regimen should be adjusted accordingly when used clinically. East Asians had longer OS and higher 5-year OS rate after treatment with a paclitaxel-platinum-based regimen than non-East Asians. Moreover, the ORR significantly improved. However, the incidence of AEs was relatively high in the East Asian population owing to low tolerance.

Abbreviations

AEs, adverse effects; 95%CI, 95% confidence interval; ECOG PS, Eastern Cooperative

Oncology Group performance status; MBMA, model-based meta-analysis; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors have declared that no competing interests exist

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Authors' contributions

Chenyang Zhao conceived the study and drafted the manuscript. All authors revised the manuscript. All authors read and approved the final manuscript.

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Figures

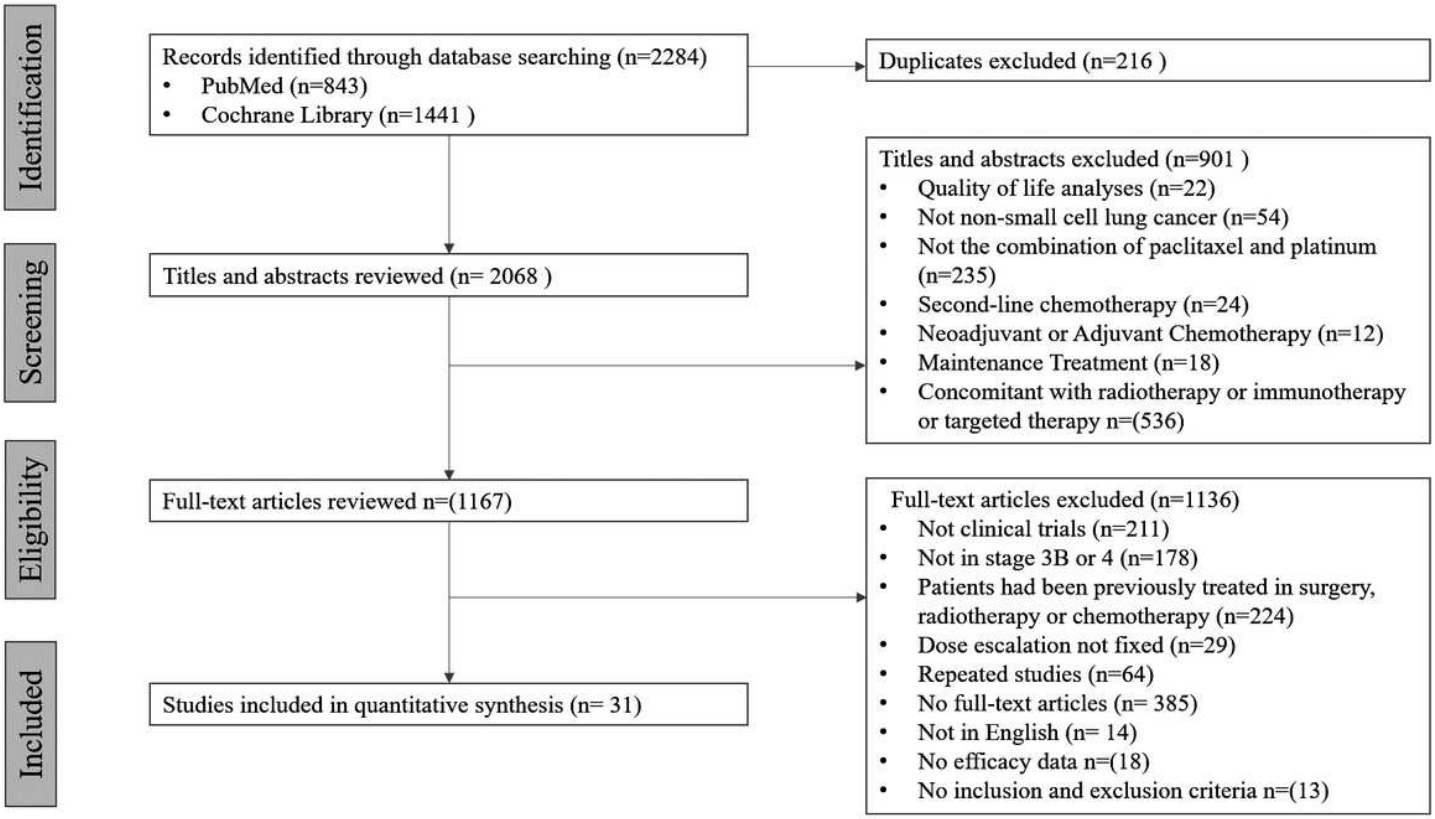

Figure 1

Flow chart of the systematic reviews' inclusion.

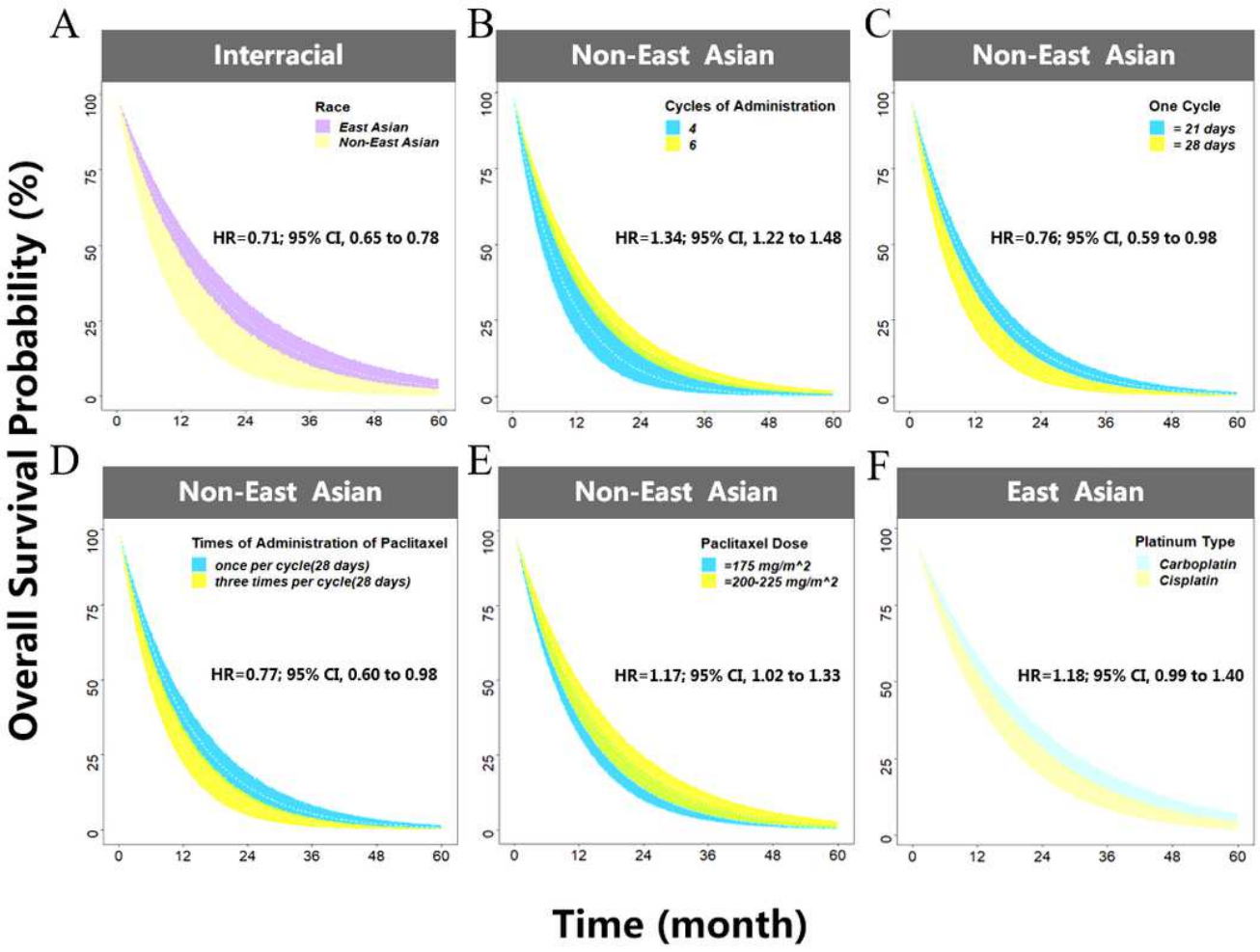

Figure 2

Predicted OS curve (and its 95% CI) of different racial groups and typical schedules. The shadow represents 95% CIs of OS. The dotted line represents model-predicted 50th percentiles of OS. (A) East Asians versus Non-East Asians (B) 4 versus 6 cycles of chemotherapy in Non-East Asian (C) 21 days per cycle versus 28 days in Non-East Asian (D) Paclitaxel administered 1 versus 3 times per cycle in Non-East Asian (E) Paclitaxel 175 mg/m2 versus 200–225 mg/m2 in Non-East Asian; (F) Carboplatin versus cisplatin in East Asian.

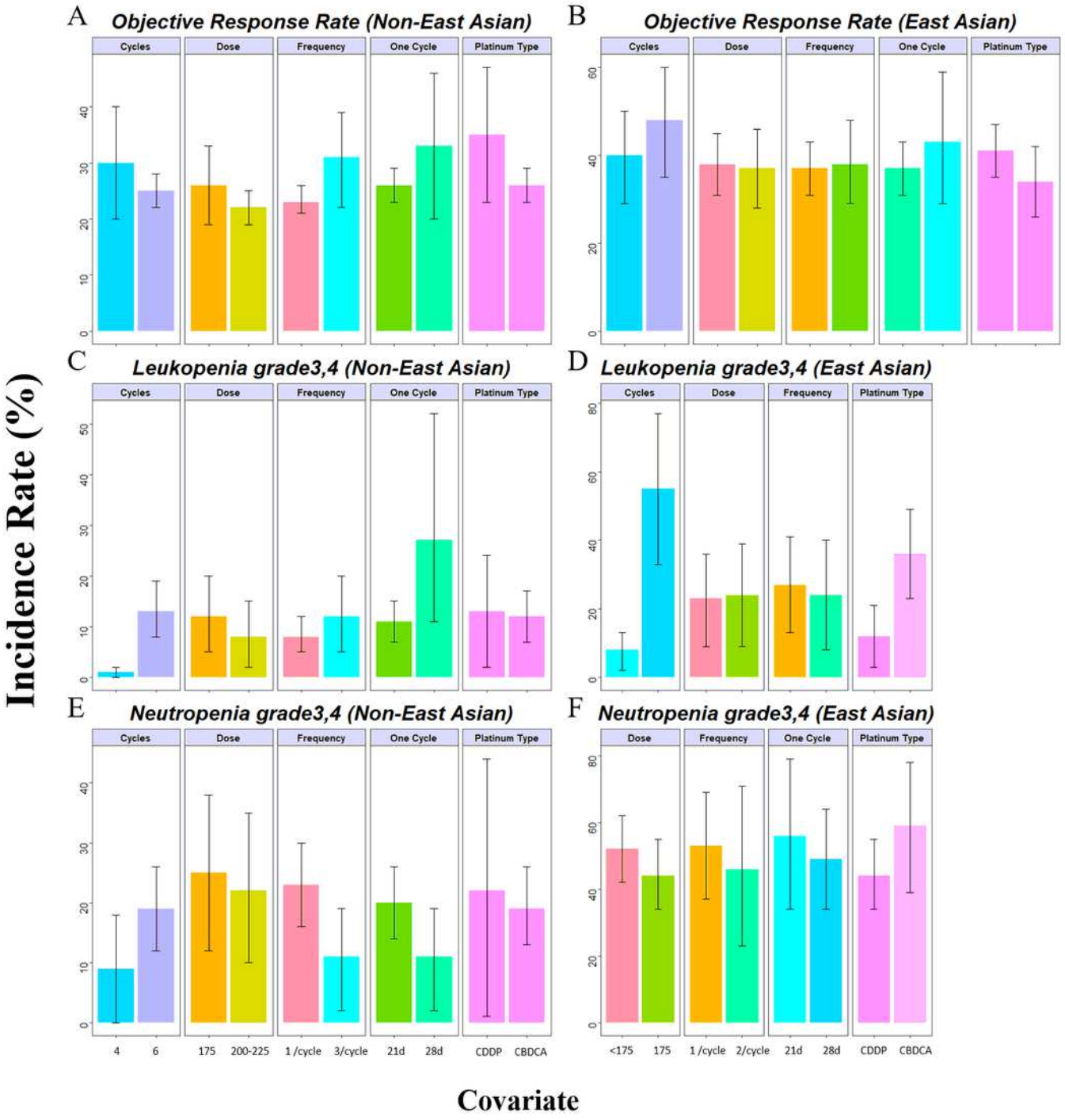

Figure 3

Visualization results of ORR and grade 3-4 AEs at different covariate levels in subgroup meta-analysis. Error bars represent 95% CI based on meta-analysis. Cycles, cycles of chemotherapy; Dose, paclitaxel doses, Frequency, times of administration of paclitaxel; One cycle, duration (days) of one cycle;21d, 21days; 28d, 28days; CDDP, cisplatin; CBDCA, carboplatin. Different covariate levels were divided into cycles of chemotherapy (4 versus 6), paclitaxel dose (175 mg/m2versus 200–225 mg/m2,<175 mg/m2

versus 175 mg/m2), times of administration of paclitaxel(1/cycle versus 3/cycle,1/cycle versus 2/cycle), duration (days) of one cycle(21days versus 28days), platinum type(cisplatin versus carboplatin).

Supplementary Files

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