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SYSTEMATIC REVIEW

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Sex difference in response to non-small cell lung cancer immunotherapy: an updated meta-analysis

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ABSTRACT

Background: Studying sex differences in the efficacy of immunotherapy may contribute to the practice of the precision medicine, especially in non-small cell lung cancer (NSCLC), a kind of cancer with sexual bimorphism.

Methods: Published randomized controlled trials (RCTs), published by PubMed, Medline, Embase, and Scopus, before 15 June 2022, testing immunotherapy (CTLA-4 or PD-1/L1 inhibitor alone, combination or with chemotherapy) versus non-immunotherapy (receiving chemotherapy or placebo only) were included to assess different efficacy between males and females. The primary endpoint was overall survival (OS). This meta-analysis was registered with PROSPERO (CRD42022298439).

Results: Sixteen RCTs, involving 10,155 patients with advanced NSCLC, was collected in this meta-analysis. The pooled HR comparing immunotherapy vs non-immunotherapy were 0.76 (95%CI 0.71–0.81) for males and 0.74 (95%CI 0.63–0.87) for females. The pooled HRs comparing immune-checkpoint inhibitors (ICIs) plus chemotherapy versus chemotherapy were 0.79 (95%CI 0.70–0.89) for males and 0.63 (95%CI 0.42–0.92) for females. The pooled HRs comparing ICIs versus chemotherapy were 0.74 (95%CI 0.67–0.81) for males and 0.83 (95%CI 0.73–0.95) for females. In squamous NSCLC, the pooled HRs comparing immunotherapy vs non-immunotherapy were 0.73 (95%CI 0.58–0.91) for males and 0.74 (95%CI 0.37–1.48) for females. In non-squamous NSCLC, the pooled HRs comparing immunotherapy versus non-immunotherapy were 0.62 (95%CI 0.71–0.94) for males and 0.59 (95%CI 0.39–0.89) for females.

Conclusion: Compared to chemotherapy, immunotherapy can improve the prognosis of patients with advanced NSCLC. Meanwhile, there are sex differences in the efficacy of immunotherapy.

KEY MESSAGE

- Compared to chemotherapy, immunotherapy can improve the prognosis of patients with advanced NSCLC.
- The most interesting thing in this study is that immunotherapy showed significant sex differences in the treatment of squamous NSCLC.

Abbreviations: CI: confidence interval; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; EGFR: epidermal growth factor receptor; HR: hazard ratios; ICIs: immune-checkpoint inhibitors; NSCLC: non-small cell lung cancer; OS: overall survival; PD-1: programmed death 1; PD-L1: programmed death ligand 1; RCT: randomized controlled trials; TNBC: triple-negative breast cancer

1. Introduction

Immunotherapy is defined as the use of materials that augment and/or re-establish the immune system's ability to prevent and fight disease [1]. It is well known that immune system functions and immune responses differ in male and female [2]. This is associated with complex interactions between genetic, hormones, behavioural traits, and symbiotic microbial composition. Previous studies have noted that this difference is also reflected in the response to

immunotherapy with cancer patients [3]. In 2017, Botticelli et al. reported a trend towards increased benefits for male patients treated with immune-checkpoint inhibitors (ICIs). This meta-analysis included eight studies on melanoma, 6 on non-small cell lung cancer (NSCLC), 1 on renal cells, 1 on head and neck tumours and 1 on urothelial carcinoma [4]. As the therapeutic effects of ICIs varies between males and females, sex may have the potential to be a natural biomarker in solid cancers and the effect of sex differences on immunotherapy is worth exploring.

Increasing literature points to sex differences in the immune system. Sex-related differences in survival benefits were studied by Conforti et al. [5], demonstrating that men receive greater benefit from cancer immunotherapy than women. Wallis et al. [6] have reported conflicting results, who found no statistically significant association between patient sex and the magnitude of benefit from advanced cancer immunotherapy. However, the specific effect of sex on the efficacy of immunotherapy in patients with lung cancer still remains unclear.

Lung cancer is current the second most diagnosed tumour with its mortality rate ranks the first around the world. The vast majority of lung cancer is NSCLC [7]. In addition, NSCLC was found to be a tumour in the presence of a sexual dimorphism [8]. Therefore, it is very necessary to study the sex effect in therapeutic efficacy in NSCLC patients. The types of immunotherapy include vaccines, antibody therapies, ICIs, oncolytic virus therapy, chimeric antigen receptor T-cell therapy, etc. Among the ICIs, programmed cell death 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte protein 4 (CTLA-4) are the most well-represented [1]. Herein, this meta-analysis was conducted to study the therapeutic differences in ICIs (PD-1, PD-L1 or CTLA-4) between males and females in NSCLC patients in order to explore the application scheme of immunotherapy in clinical practice.

2. Methods

2.1. Retrieval strategy and inclusion criteria

This meta-analysis was performed under the guidance of the PRISMA guidelines and registered with PROSPERO (CRD42022298439). Phase 2 and 3 randomized controlled trials (RCT), published by PubMed, medline, embase, and Scopus, before 15 June 2022, and related to NSCLC and ICIs, were searched for our meta-analysis. Two researchers searched the databases independently. The retrieval word was ("nivolumab" OR "ipilimumab" OR "sintilimab" OR "tislelizumab" OR "cemiplimab" OR "camrelizumab" OR "BMS 936558" OR "BMS 936559" OR "pembrolizumab" OR "lambrolizumab" OR "MK 3475" OR "pidilizumab" OR "CT 011" OR "durvalumab" OR "MEDI 4736" OR "atezolizumab" OR "MPDL 3280a" OR "avelumab" OR "AMP 224" OR "PD-1" OR "PD-L1" OR "B7-H1" OR "CD274" OR "programmed death 1" OR "programmed death ligand 1" OR "CTLA-4 Antigen"[Mesh]) AND ("lung tumour" OR "lung cancer" OR "lung carcinoma" OR "lung neoplasm" OR "lung malignancy" OR "lung sarcoma" OR "Lung Neoplasms"[Mesh] OR "Carcinoma, Non-Small-Cell Lung" OR "squamous cell lung carcinoma" OR "lung adenocarcinoma " OR "large cell lung carcinoma"). In addition, we reviewed the References and Supplementary materials for the final searched articles.

All the final included studies should include the programmed cell death protein 1 (PD-1) or programmed cell death 1 ligand (PD-L1) or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors in the treatment of intervention group, while the control group contained no ICIs, and the prognosis according to the sex of the patients should be provided. In addition, the included studies needed to meet the following criteria. (a) Type of study: phase II/III RCTs; (b) patients: advanced or metastatic NSCLC that cannot be treated by surgery. The following types of studies were excluded. (a) Non-English articles; (b) studies containing cancers beyond NSCLC; (c) studies unable to obtain the full article; (d) studies with survival prognosis that not able to be analyzed. For studies that have published multiple reports, only the latest or most complete reports were chose for further analysis.

2.2. Data fetch

Two researchers independently extracted the following information from each study: (a) year of publication, author, study stage, line of treatment, treatment, and median follow-up time; (b) number of patients, sex, and tumour histological type; (c) the long-term survival prognosis of the males patients and female patients, respectively.

2.3. Quality evaluation

The quality of the included clinical trials was assessed through the Cochrane collaboration tool. Each eligible study was mainly evaluated in six aspects: (a) the sequence generation; (b) allocation concealment; (c) blinding; (d) incomplete outcome data; (e) selective outcome reporting; (f) free of other bias. Each section

was rated as "low risk," "high risk" or "unclear risk". The Revman software was used to visualize the results of the article quality evaluation

2.4. Data analysis and statistical methods

The pooled hazard ratios (HR) and 95% confidence interval (CI) was used to assess the therapeutic outcomes between the intervention and control groups. Heterogeneity between studies was assessed by the I^2 statistics and I^2 value more than 50% is an indication of significant heterogeneity. Subgroup analyses were performed to investigate the sources of heterogeneity. Considering the complexity of baseline level and therapeutic regimen, random effects model was applied to improve the reliability of the results in this article. Sensitivity analysis was used to test the stability of the results. The Egger's test was used to test if the included studies had a publication bias ($p < .1$). The above analysis was performed using the Stata software. All of the p-values reported were two-sided and $p < .05$ was considered as to be statistically different, unless otherwise stated.

3. Result

3.1. Included studies and their characteristics

Under the guidance of the PRISMA guidelines, after obtaining 5569 studies through the search strategy, 257 potentially relevant articles were selected. After a summary and full-text review, 16 RCTs [9–24] met the inclusion criteria (Figure 1). Of these RCTs, 6 RCTs studied with chemotherapy plus ICIs vs chemotherapy, 9 RCTs with ICIs vs. chemotherapy, and 1 RCT with ICIs vs placebo. Meanwhile, these RCTs included 8 of PD-1 inhibitors (3 nivolumab, 5 pembrolizumab), 5 PD-L1 inhibitors (3 atezolizumab, 1 avelumab, 1 durvalumab), 1 CTLA-4 inhibitors (ipilimumab), and 2 PD-1 + CTLA-4 inhibitors (nivolumab + ipilimumab) (Table 1). Publication dates ranged from 2015 to 2021. All trials were phase 3 RCTs, of which 10 were in first-line treatment stages and others 6 were in non-first line. Three studies only included patients with squamous NSCLC, while 4 studies were only involved with patients with non-squamous NSCLC.

The number of patients included in each trial ranged between 262 and 1225. A total of 10,155 patients were included, containing 6785 male patients
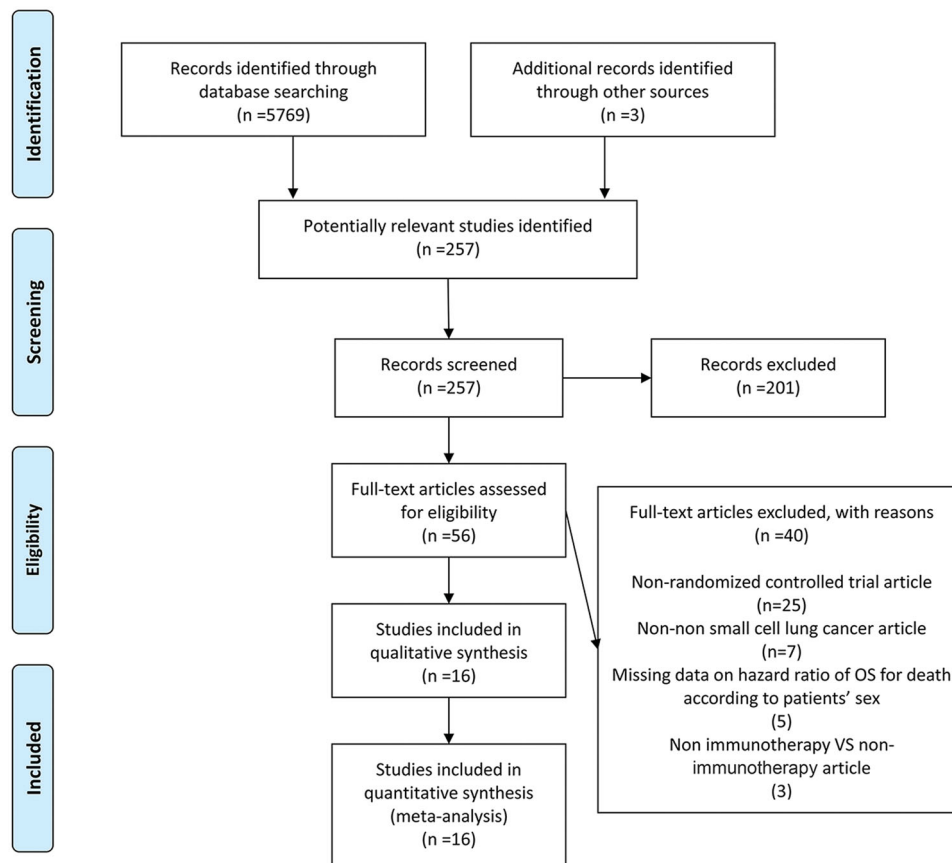

Figure 1. A schematic flow for the selection of articles included in this meta-analysis.

Table 1. Characteristics of included clinical trials in the meta-analysis.

Author, year	Trial phase	Line	Histotype	Agent of immunotherapy	Number of patients		Therapeutic regimen		Number of inclusions		Median follow-up time
					Male	Female	Treatment	Control	Treatment	Control	
Brahmer J et al., 2015	3	Non-first	Sq	PD-1	208	64	Nivolumab	Docetaxel	135	137	11+ months
Borghaei H et al., 2015	3	Non-first	Non-sq	PD-1	319	263	Nivolumab	Docetaxel	292	290	18 months
Carbone DP et al., 2017	3	First	All	PD-1	332	209	Nivolumab	Chemotherapy	271	270	13.5 months
Govindan R et al., 2017	3	First	Sq	CTLA-4	635	114	Ipilimumab + chemotherapy	Placebo + chemotherapy	388	361	12.5 months
Fehrenbacher L et al., 2018	3	Non-first	All	PD-L1	758	467	Atezolizumab	Docetaxel	613	612	21 months
Barlesi F et al., 2018	3	Non-first	All	PD-L1	367	162	Avelumab	Docetaxel	264	265	17.8+ months
Gandhi L et al., 2018	3	First	Non-sq	PD-1	363	253	Pembrolizumab + chemotherapy	Placebo + chemotherapy	410	206	10.5 months
Paz-Ares L et al., 2018	3	First	Sq	PD-1	455	104	Pembrolizumab + chemotherapy	Placebo + chemotherapy	278	281	7.8 months
West H et al., 2019	3	First	Non-sq	PD-L1	400	279	Atezolizumab + chemotherapy	Chemotherapy	451	228	18.5+ months
Reck M et al., 2019	3	First	All	PD-1	187	118	Pembrolizumab	Chemotherapy	154	151	25.2 months
Hellmann MD et al., 2019	3	First	All	PD-1 + CTLA-4	515	278	Nivolumab + ipilimumab	Chemotherapy	396	397	29.3+ months
Herbst RS et al., 2020	2/3	Non-first	All	PD-1	634	399	Pembrolizumab	Docetaxel	690	343	42.6 months
Wu YL et al., 2021	3	First	All	PD-1	224	38	Pembrolizumab	Chemotherapy	128	134	33.0 months
Nishio M et al., 2021	3	First	Non-sq	PD-L1	384	194	Atezolizumab + chemotherapy	Chemotherapy	292	286	14.8 months
Faivre-Finn C et al., 2021	3	Non-first	All	PD-L1	500	213	Durvalumab	Placebo	476	237	34.2 months
Paz-Ares L et al., 2021	3	First	All	PD-1 + CTLA-4	504	215	Nivolumab + ipilimumab + chemotherapy	Chemotherapy	361	358	13.2 months

sq: squamous; non-sq: non-squamous; PD-1: programmed cell death protein 1; PD-L1: programmed cell death 1 ligand 1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4.

(66.8%) and 3370 female patients (33.2%). The intervention group included 5599 (55.1%) patients and 4556 (44.9%) patients were included in the control group. In all studies, the median follow-up time varies between 7.8 and 42.6 months. All studies reported an overall survival (OS)-related HR based on the sex of the patient.

Randomized treatment assignment sequences were generated in all trials, two among which were double-blind trials. In addition, control groups of 4 trials used placebo to rule out placebo effects potentially triggered by ICIs. The clinical trials were evaluated using the Cochrane collaboration tool and the results were showed in Supplementary Figures 1 and 2.
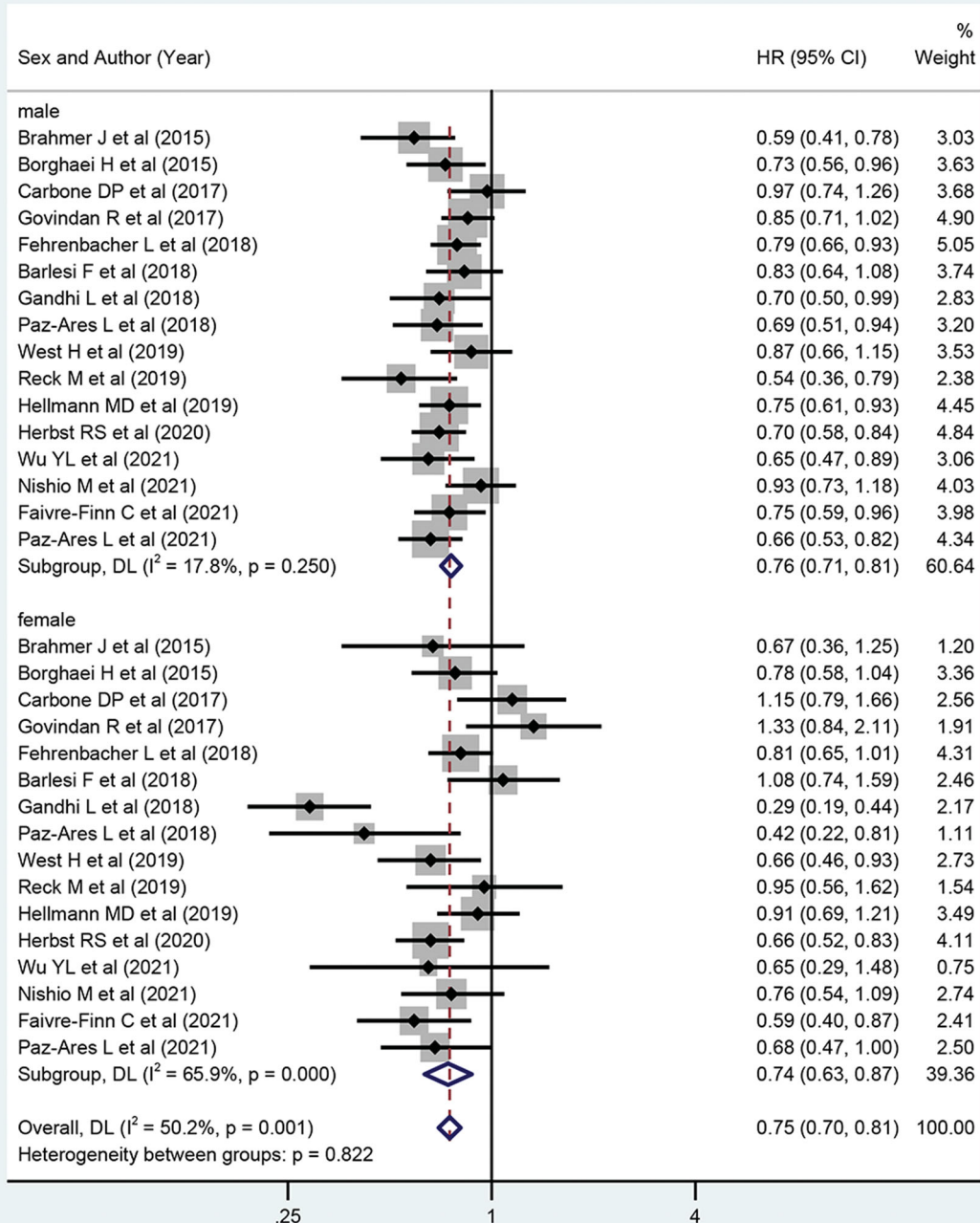
3.2. Treatment effect of ICIs in male and female

Overall, compared with patients not receiving ICIs (receiving chemotherapy or placebo only), the OS for patients receiving ICIs alone, combination (CTLA-4 + PD-1/L1) or with chemotherapy were all significantly prolonged (HR: 0.75, 95%CI 0.70–0.81; I^2=50.2%; Figure 2). Meanwhile, both in males (HR: 0.76, 95%CI 0.71–0.81; I^2=17.8%; Figure 2) and females (HR: 0.74, 95%CI 0.63–0.87; I^2=65.9%; Figure 2), those who received ICIs (with or without chemotherapy) had longer OS than those who did not receive ICIs.

3.3. Subgroup analysis

When control group was limited to chemotherapy, the results of the subgroup analysis based on whether the intervention group contains chemotherapy are shown in Figure 3. Overall, compared with chemotherapy alone, ICIs with (HR: 0.71, 95%CI 0.60–0.84) or without (HR: 0.77, 95%CI 0.72–0.84) chemotherapy were able to improve OS in NSCLC patients. For ICIs combined with chemotherapy, both males (HR: 0.79, 95%CI 0.70–0.89) and females (HR: 0.63, 95%CI 0.42–0.92) could benefit from ICIs combined with chemotherapy comparing with chemotherapy alone. For ICIs without combination with chemotherapy, both males (HR: 0.74, 95%CI 0.67–0.81) and females (HR: 0.83, 95%CI 0.73–0.95) could benefit from ICIs compared to chemotherapy alone. It seemed that females benefitted more from the ICIs & chemotherapy combination than males, while males benefitted more from ICIs without chemotherapy than females.

A subgroup analysis based on the patient's treatment stage was also performed, and the results are shown in Figure 4. Overall, ICIs with or without chemotherapy can improve OS, no matter in first-line
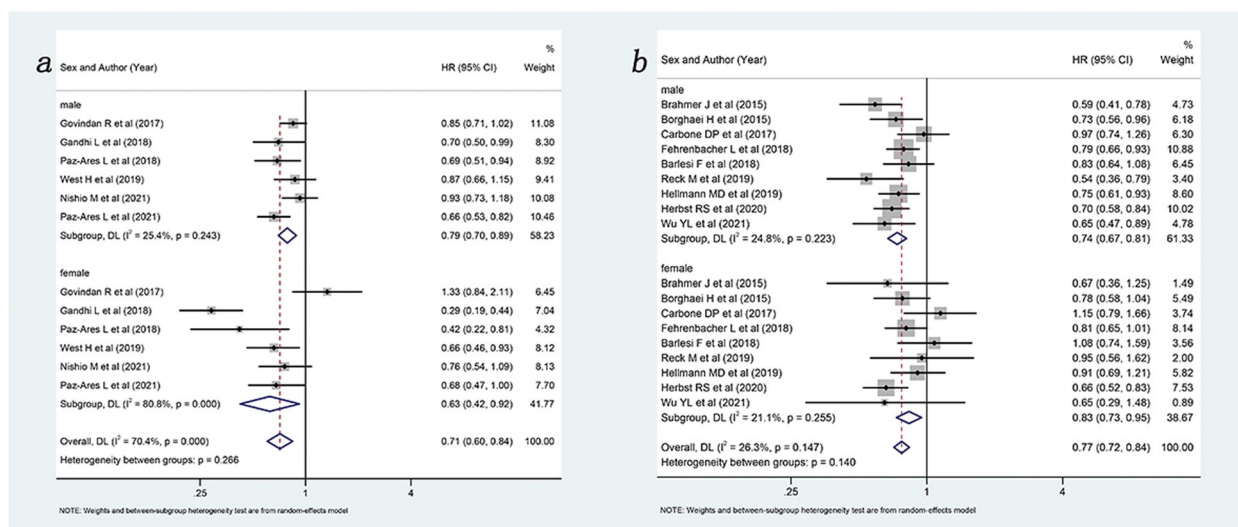
Figure 2. Forest plot of comparison: overall survival of patients receiving ICIs alone or with chemotherapy versus patients not receiving ICIs (receiving chemotherapy or placebo only) (male: $p < .001$, female: $p < .001$, overall: $p < .001$).

(HR: 0.75, 95%CI 0.87–0.85) or non-fist line (HR: 0.75, 95%CI 0.69–0.80), compared with control group (chemotherapy or placebo). In the first line, both males (HR: 0.77, 95%CI 0.69–0.85) and females (HR: 0.73, 95%CI 0.56–0.96) could benefit from ICIs with or without chemotherapy compared with the control group. In the non-first line, both males (HR: 0.74,

95%CI 0.68–0.81) and females (HR: 0.75, 95%CI 0.65–0.68) also could benefit from ICIs with or without chemotherapy compared with the control group.

Then, a subgroup analysis of the treatment effects of PD-1 inhibitor and PD-L1 inhibitors was performed, and the results are shown in Figure 5. Overall, compared with control group, ICIs with or without

Figure 3. Forest plot of comparison based on whether the intervention group contains chemotherapy. (a) Overall survival of patients receiving ICIs plus chemotherapy versus patients receiving chemotherapy alone (male: $p < .001$, female: $p = .018$, overall: $p < .001$). (b) Overall survival of patients receiving ICIs versus patients receiving chemotherapy alone (male: $p < .001$, female: $p = .005$, overall: $p < .001$).
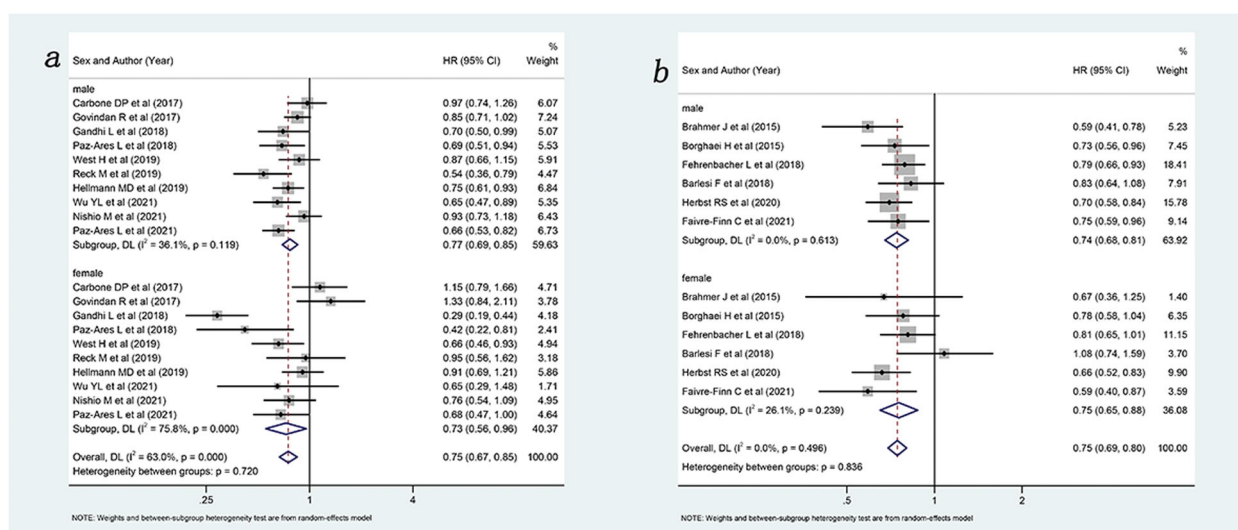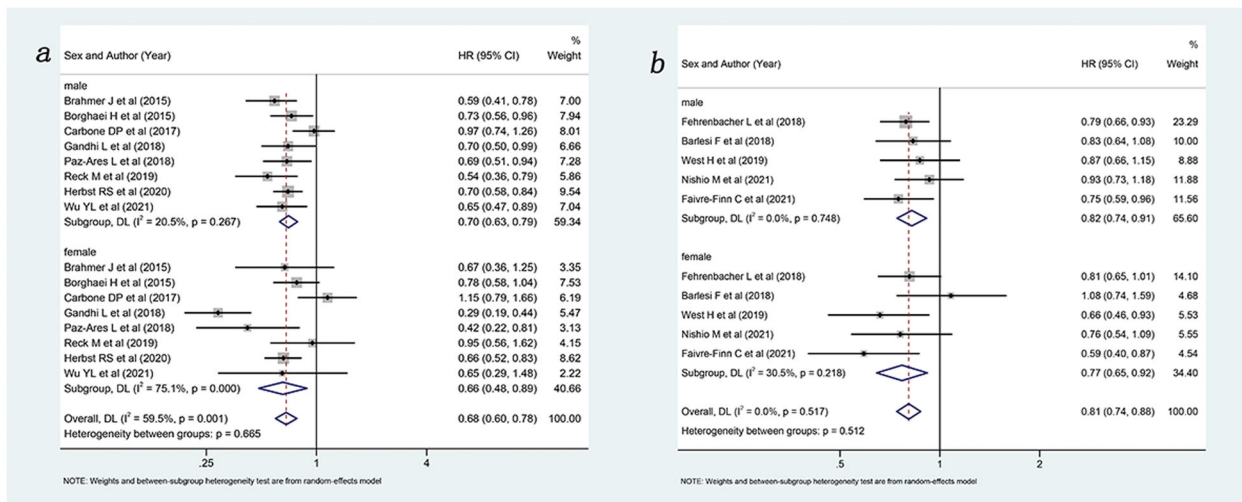

Figure 4. Forest plot of comparison based on treatment stage. (a) Overall survival of patients receiving ICIs with or without chemotherapy versus patients not receiving ICIs (receiving chemotherapy or placebo only) in first line (male: $p < .001$, female: $p = .023$, overall: $p < .001$). (b) Overall survival of patients receiving ICIs with or without chemotherapy versus patients not receiving ICIs (receiving chemotherapy or placebo only) in non-first line (male: $p < .001$, female: $p < .001$, overall: $p < .001$).

chemotherapy improved OS, whether as PD-1 inhibitors (HR: 0.68, 95%CI 0.60–0.78) or as PD-L1 inhibitors (HR: 0.81, 95%CI 0.74–0.88). Among the PD-1 inhibitor, both males (HR: 0.70, 95%CI 0.63–0.79) and females (HR: 0.66, 95%CI 0.48–0.89) could benefit from ICIs with or without chemotherapy compared with the control group. Among the PD-L1 inhibitors, both males (HR: 0.82, 95%CI 0.74–0.91) and females (HR: 0.77, 95%CI 0.65–0.92) could also benefit from intervention group compared with the control group. It was important to note that treatment with PD-1

inhibitor appears superior to PD-L1 inhibitor in males and females.

Lastly, a subgroup analysis based on the histological type of the included patients was performed, and the results are shown in Figure 6. Overall, compared with no ICIs, ICIs with or without chemotherapy were able to improve OS, whether for squamous (HR: 0.74, 95%CI 0.58–0.94) or non-squamous (HR: 0.70, 95%CI 0.57–0.86) NSCLC patients. In patients with non-squamous NSCLC, both males (HR: 0.82, 95%CI 0.71–0.94) and females (HR: 0.59, 95%CI 0.39–0.89)

Figure 5. Forest plot of comparison based on the type of ICIs. (a) Overall survival of patients receiving PD-1 inhibitor with or without chemotherapy versus patients not receiving ICIs (receiving chemotherapy or placebo only) (male: $p < .001$, female: $p = .006$, overall: $p < .001$). (b) Overall survival of patients receiving PD-L1 inhibitor with or without chemotherapy versus patients not receiving ICIs (receiving chemotherapy or placebo only) (male: $p < .001$, female: $p = .003$, overall: $p < .001$).
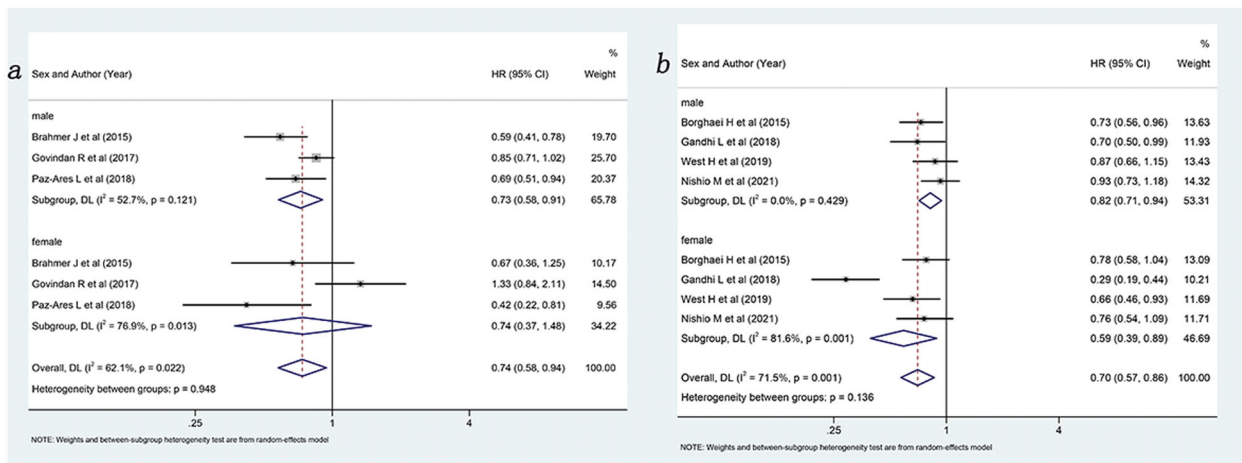
Figure 6. Forest plot of comparison based on histological type. (a) Overall survival of patients receiving ICIs with or without chemotherapy versus patients not receiving ICIs (receiving chemotherapy or placebo only) in squamous NSCLC (male: $p = .005$, female: $p = .400$, overall: $p = .015$). (b) Overall survival of patients receiving ICIs with or without chemotherapy versus patients not receiving ICIs (receiving chemotherapy or placebo only) in non-squamous NSCLC (male: $p = .005$, female: $p = .011$, overall: $p = .001$).

could benefit more from ICIs with or without chemotherapy compared with the control group. Notably, in squamous, males benefitted more from ICIs (with or without chemotherapy) than the control group (HR: 0.73, 95%CI 0.58–0.91) while females did not (HR: 0.74, 95%CI 0.37–1.48).

3.4. Sensitivity analysis and publication bias

Sensitivity analysis showed results were stable in the HR of OS comparing immunotherapy (CTLA-4 or PD-1/L1 inhibitor alone, combination or with chemotherapy) to non-immunotherapy (receiving chemotherapy or placebo only) (Supplementary Figure 3). The Egger's test showed that there was no statistically significant publication bias in the study findings included in this meta-analysis ($p = .311$, Supplementary Figure 4).

4. Discussion

Curing cancer through precision medicine is the overarching goal of a new wave of molecular and genomic therapies. Precision medicine relies on biomarker discovery and research [25]. Sex can also be considered as a biomarker since there are clear differences in genes and lifestyle habits between males and females

[26,27]. In NSCLC, a kind of cancer with sexual dimorphism, the role of sex as potential biomarker may be particularly evident [28]. The sex differences between males and females with NSCLC are reflected in many aspects: (1) the median age of females at diagnosis is lower than males; (2) the tobacco contact history of females is generally less than that of males; (3) in females and males with similar tobacco exposure, lung cancer occurs earlier in females [29,30]; (4) the major histological subtype in females is adenocarcinoma, while in males is squamous; (5) females usually have better outcomes than males at all stages of diagnosis; (6) epidermal growth factor receptor (EGFR) mutations is more common in females [31,32]. However, in the existing clinical treatment options, sex is rarely used as the basis for choosing the treatment options. Therefore, the role of sex in the treatment of NSCLC needs to be further explored.

In this meta-analysis, although the ICIs, compared to chemotherapy, could improve OS in NSCLC, the females seemed to benefit more from chemotherapy plus ICIs than males, and males seemed to benefit more from ICIs alone than females. Similar results were also found by Conforti et al. [33], in whose study, females with advanced lung cancer experience a larger benefit from the addition of chemotherapy to an anti-PD-1 or PD-L1 than males while males show greater efficacy of anti-PD-1 alone than females. Since the single-agent immunotherapy included in Conforti study contained only the case of PD-1 inhibitors, our studies that including PD-1, PD-L1 and CTLA-4 inhibitors could be considered necessary complementary and complete. Moreover, our study included the larger number of NSCLC patients (10,155 patients), coming from 16 RCT pairs, which increased the credibility of our analysis.

In addition to the evidence from the clinical experiments, numerous preclinical studies have also revealed an association between sex differences and lymphocytes. For example, Liva et al. found that testosterone can act directly to increase IL-10 gene expression *via* the androgen receptor on CD4 + T lymphocytes [34]. The effects of ICIs depends on immune priming of peripheral lymphoid tissues. Besides, by analyzing patient data, Conforti et al. found that females responses to pembrolizumab may be less than males [35]. These may be the biological principles that support males patients may benefit more from ICIs alone than females.

As for another therapeutic regimen that is included in this article, the association of chemotherapy plus immunotherapy with better prognosis in female patients has ever been found in triple-negative breast cancer (TNBC). The clinical effect showed that the combination regimen of PD-1/L1 inhibitor plus chemotherapy had a higher success rate in metastatic TNBC (mTNBC) than ICIs alone [36]. Biological studies show that ICIs combined with chemotherapy have the potential to enhance the recognition and elimination of tumour cells by the immune system [37]. Squamous, the main type of NSCLC in male patients, responds poorer to chemotherapy, and lung adenocarcinoma, the main type of NSCLC in female patients, is more sensitive to chemotherapy. Therefore, the sex differences in ICIs plus chemotherapy treatment patterns in the two sexes may mainly stem from the difference in benefit in chemotherapy. Indeed, studies have attributed the poor immunotherapy outcomes observed in female patients to weaker antigenicity in females, and chemotherapy is thought could increase the mutational load of tumours and thus increase the antigenicity of tumour cells [26]. However, the results can only show that males and females benefit differently under different treatment regimens. It is not clear the immunotherapy regimen that females or males could benefit most is ICIs alone or combined with chemotherapy. Therefore, RCTs in males and females compared ICIs alone to ICIs combination chemotherapy may be warranted.

Besides whether immunotherapy should be combined with chemotherapy, whether immunotherapy should be used in the first line is also a question worth clinical attention [38]. By subgroup analysis according the line of treatment, it was found that whether in the first or non-first-line, males and females have a better benefit in immunotherapy (ICIs alone or together with chemotherapy), compared with the control group. Moreover, there were no significant sex differences in the performance of immunotherapy (ICIs alone or together with chemotherapy) in both first-and and non-first-line treatments. The study by Ruiz Patino et al. [39] also supports that immunotherapy with any treatment line of therapy can improve survival in patients with advanced metastatic NSCLC. However, from the perspective of clinical application, first-line patients are supposed to have better immune system function and stronger physical function than non-first-line patients, which may help lower the adverse effects and improve the treatment effect. Therefore, immunotherapy may be more meaningful in first-line treatment.

With the rapid development of immunotherapy, both in first and non-first-line therapy, there are different types of ICIs in clinical use. Among them, the

most widely used and the most dominant types are PD-1 and PD-L1 inhibitors. By subgroup analysis according the inhibitor type, no significant difference in benefit using PD-1 or PD-L1 inhibitors. However, it can be found that PD-1 inhibitors appear to work better than PD-L inhibitors in both males and females. Theoretically, PD-1 antibodies can bind to the PD-1 protein on T cell membranes, which would block the binding between both PD-1 and PD-L1/PD-L2. However, the PD-L1 antibody can only interact with PD-L1 and specifically blocks the binding between PD-1 and PD-L1. Therefore, after using the anti-PD-L1 treatment, the interaction between PD-1 and PD-L2 may still inhibit T cells. This may explain the greater potential of PD-1 inhibitors than PD-L1 inhibitors in the treatment of NSCLC patients. Note that the large sample size gap between the PD-1 and PD-L1 subgroup analysis may influence result in the study. The number of PD-1 related studies is much larger than PD-L1 related studies because of the early launch time of PD-1. In this study, eight PD-1 studies were included, involving 8340 patients and five PD-L1 studies were included, involving 1315 patients. Therefore, richer clinical experimental data are needed to support more accurate and convincing results.

The most interesting thing in this study is that immunotherapy showed significant sex differences in the treatment of squamous NSCLC. Possible explanations were tried to be given in terms of both genetic and behavioural differences between the sexes. Females and males differ in early-stage transcriptomic biomarkers and cell-lineage gene of squamous NSCLC [40]. For instance, the sex-determining region Y-Box 2 (SOX2) [41] is a potential cell lineage gene highly expressed in the pathogenesis of squamous NSCLC. Those sex-related genes like Y-Box 2 (SOX2) may be the gene hierarchy responsible for sex differences. In terms of behavioural habits, males have more tobacco applicability than females. Studies have shown that in squamous patients, light smokers are associated with more female patients, more advanced tumours, and worse prognosis than gravity smokers [42,43]. Therefore, it may be the poor prognosis of squamous NSCLC in females that results in worse benefit from immunotherapy in females than in males. But the deeper biological principles remain to be explored.

Although female and male patients with squamous NSCLC showed significant differences in benefit from immunotherapy, it has to be admitted that great heterogeneity was found in the subgroup analysis for squamous females ($I^2=76.9\%$, $p=.013$). The experimental groups in the three included studies were

nivolumab (Brahmer J), ipilimumab + chemotherapy (Govindan R), and pembrolizumab + chemotherapy (Paz-Ares L). It can be found that CTLA-4 inhibitors (ipilimumab) performed the worst in female squamous NSCLC treatment (HR: 1.33, 95%CI 0.84–2.11), which may be the critical to outcomes. In some published studies, a higher benefit from anti-CTLA-4 was found in males compared to females [44]. The significant sex differences in the effects of anti-CTLA-4 may influence the conclusion that males benefit more from immunotherapy (ICIs alone or with chemotherapy) than females in squamous NSCLC. Therefore, it is necessary to replicate this finding in a larger cohort of squamous NSCLC patients.

Honestly, this study has some limitations. First, most RCTs did not report OS according to sex, which largely limited the number of RCTs that we included. Second, in the RCTs included in our study, the vast majority of non-immunotherapy control groups were chemotherapy, which narrowed the scope of non-immunotherapy in a practical sense.

5. Conclusion

To conclude, appropriate biomarkers, on the one hand, can help to facilitate a more effective selection of those patients who could truly benefit from ICIs. On the other hand, it may be beneficial to select the most appropriate treatment strategy for patients to achieve precision medicine. In our study, immunotherapy for squamous NSCLC performed significantly better in males than in females. It would be a good choice for future studies to explore different immunotherapy regimens for males and females, which may be beneficial to help patients choose the most appropriate treatment strategy.

Acknowledgement

Author contributions

Dina Guo designed the research process. Jiali Liang and Jiaze Hong searched the database for corresponding articles and drafted the meta-analysis. Xin Tang and Xinyi Qiu extracted useful information from the articles above. Keying Zhu used statistical software for analysis. Liyuan Zhou used statistical software for analysis and polished this article. All authors had read and approved the manuscript and ensured that this was the case.

Disclosure statement

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