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Comparative clinical outcomes and predictive biomarkers of sintilimab combinations *vs.* single therapy in cancer: a systematic review and meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: This study aimed to compare the efficacy and safety between sintilimab combinations and single treatment in cancer patients, as well as identify biomarkers for selection of patients who might benefit from the combination treatments.

MATERIALS AND METHODS: A search of randomized clinical trials (RCTs) comparing sintilimab combinations *vs.* single treatment in different tumors according to the PRISMA guidelines was performed. Selected endpoints included completion response rate (CR), objective response rate (ORR), disease control rate (DCR), overall survival (OS), progression-free survival (PFS), major adverse effects (AEs), immune-related adverse events (irAEs). Subgroup analyses based on different combination regimens, tumor type and basic biomarkers were included.

RESULTS: Results reported from 11 RCTs involving 2,248 patients were included in this analysis. Pooled results indicated that both sintilimab plus chemotherapy and sintilimab plus targeted therapy significantly improved CR [RR=2.44, 95% CI (1.14, 5.20), *p*=0.021; RR=2.91, 95% CI (1.29, 6.57), *p*=0.010], ORR [RR=1.34, 95% CI (1.13, 1.59), *p*=0.001; RR=1.70, 95% CI (1.13, 2.56), *p*=0.011], PFS [HR=0.56, 95% CI (0.43, 0.69), *p*<0.001; HR=0.56, 95% CI (0.49, 0.64), *p*<0.001] and OS [HR=0.59, 95% CI (0.48, 0.70), *p*<0.001]. Subgroup analyses suggested that the sintilimab-chemotherapy group exhibited a superior PFS benefit than the chemotherapy alone group regardless of age, gender, EGOS PS, PD-L1 expression, smoking status, and clinical stage. There were no significant statistical differences in the incidence of any grade and grade 3 or worse AEs between the two groups [RR=1.00, 95% CI (0.91, 1.10), *p*=0.991; RR=1.06, 95% CI (0.94, 1.20), *p*=0.352]. While the incidence of any grade irAEs was higher with sintilimab plus chemotherapy as compared to chemotherapy alone (RR=1.24, 95% CI (1.01, 1.54), *p*=0.044), but no significant difference was found for grade 3 or worse irAEs (RR=1.11, 95% CI (0.60, 2.03), *p*=0.741).

CONCLUSIONS: Sintilimab combinations brought benefits to a greater number of patients at the cost of a mild increase of irAEs. PD-L1 expression may not be used as a predictive biomarker, composite biomarkers consisting of PD-L1 and MHC class II expression are worth to be explored to enlarge the patient population that benefits from sintilimab combinations.

Key Words:
Sintilimab, Immunotherapy, Efficacy, Adverse effects, Biomarker, Meta-analysis.

Introduction

Cancer is the main cause of death and an important obstacle to extending life expectancy in every country of the world[1]. According to the global cancer statistics 2020[2], there were an estimated 19.3 million new cases and 10 million cancer deaths worldwide in 2020. Currently, cancer immunotherapy has become another important anti-tumor treatment following surgery, radiation therapy, chemotherapy, and molecular targeted therapy, which exhibited good clinical response in cancer patients[3]. However, it is reported that only a minority of patients experience long-term benefits due to the primary and secondary resistance to single drug immunotherapy[4]. The strategy of combined immunotherapy is considered to be an effective and applicable method to solve this dilemma. Specially, PD-1 inhibitors including pembrolizumab, atezolizumab plus chemotherapy regimens have become the standard

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first-line or second-line therapies for cancer patients with different tumor types[5,6]. Additionally, in order to enlarge the benefited populations, the identification of biomarkers for the selection of patients who might benefit from combinations is of great interest. Current biomarker candidates, such as PD-L1 expression and tumor mutational burden (TMB), become a research hotspot.

Sintilimab is a humanized, monoclonal antibody against PD-1 that has been approved by NMPA for the monotherapy of relapsed or refractory classical Hodgkin lymphoma, the first-line treatment of non-squamous and squamous non-small cell lung cancer (NSCLC) combined with chemotherapy, and the first-line treatment of hepatocellular carcinoma (HCC) combined with bevacizumab[7-10]. In addition, sintilimab combination therapy and monotherapy have shown potential anti-tumor efficacy in many other cancers, including cervical cancer[11], gastric cancer[12], esophageal squamous cell carcinoma[13], renal cancer[14], biliary tract cancer[15], pancreatic cancer[16] and so on. Furthermore, the sintilimab combination therapy is more likely to become a new and promising treatment option[17]. However, whether combination therapy is more effective and safer still needs to be explored. Additionally, it is also necessary to identify patients who might benefit most from immune-combination treatment. Thus, it is important to study the efficacy and safety of sintilimab combination therapy, as well as explore the biomarker candidates.

Currently, there is no systematic comparison of sintilimab combinations *vs.* single treatment for malignancies. In this study, the meta-analysis compared the efficacy and safety of sintilimab plus chemotherapy or targeted therapy *vs.* single treatment, evaluated and discussed the prognostic effects of the biomarker candidates including PD-L1 expression, TMB and MHC class II expression on cancer patients. This study will provide a reference for the clinical application and subsequent indications' development for sintilimab combination treatment, as well as provide a reference for exploring the biomarker candidates for selection of patients who might benefit from combinations.

Materials and Methods

Search Strategy

A comprehensive literature search was conducted to identify published studies of randomized controlled trials (RCTs) of sintilimab combinations *vs.* single treatment for cancer patients. Multiple databases, including PubMed, Cochrane Library, Web of Science, EMBASE, CNKI database and Wanfang database without language restriction were searched until April 2022. The keywords sintilimab, tumor, and their Medical Subject Headings (MeSH) term were used to build a search strategy. Additionally, in order to avoid omitting any relevant research, we reviewed the list of references of the retrieved research. Two investigators independently performed the literature searches.

Inclusion and Exclusion Criteria

Studies were included if (1) it was designed as RCT; (2) patients diagnosed with cancers were treated with sintilimab combinations therapies and single treatment; (3) outcomes included overall survival (OS), progression-free survival (PFS), completion response (CR), objective response rate (ORR), disease control rate (DCR), adverse events (AEs) and immune-related adverse events (irAEs). The exclusion criteria were (1) review/editoral/letter; (2) conference abstract; (3) case report; (4) retrospective study; (5) animal or *in vitro* studies; (6) unable to extract valid data.

Data Screening and Data Extraction

Duplicates exclusion was achieved by two independent reviewers. If no agreement was reached, the conflict was solved by a third reviewer. Two independent investigators extracted the following information from each article: (a) name of the first author; (b) publication time; (c) number of cases and controls for each study; (d) study design and interventions; (e) primary effectiveness index; (f) primary safety index.

Quality Assessment

The Cochrane risk of bias assessment tool was used to evaluate the methodological quality of individual studies based on the following aspects: (a) random sequence generation; (b) allocation concealment; (c) blinding of participants and personnel; (d) blinding of outcome assessment; (e) incomplete outcome data; (f) selective reporting; and/or (g) other biases. The answer of each item was high, low, or unclear risk of bias, and different opinions could be resolved by an open discussion or a third reviewer. The general chart of bias risk was made by Revman software.

Statistical Analysis

Given that various outcomes have been applied in the included studies, the pooled effects were presented as relative risk (RR) or hazard ratio (HR) and 95% confidence interval (CI). All meta-analyses and statistical analyses were performed using the Stata software (version 12.0; Stata Corporation, College Station, TX, USA). If there was no statistical heterogeneity among the studies (p> 0.1, I^2 < 50%), the fixed effects model was used for analysis; otherwise, the random effect model was used for analysis. Most of the HR values were extracted from univariate and multivariate Cox regression analyses, and a few were calculated using Kaplan-Meier curves. Revman 5.0 software (Review Manager Web, The Cochrane collaboration, Copenhagen, Denmark) was used to map the risk of publication bias, and Egg's test was used to analyze publication bias. The p-value < 0.05 was statistically significant.

Results

Systematic Literature Search

A flowchart of the study retrieval process is shown in Figure 1. A total of 1,032 potential studies were initially identified from the initial search of the aforementioned databases, of which 375 were duplicates. After removal of the duplicates and screening of the titles and abstracts, a total of 497 of the initial records remained, the full text documents of which were assessed, from which 489 were excluded. Those included: (1) review articles (n=181); (2) animal experiments (n=2); (3) case reports (n=74); (4) conference abstracts (n=75); (5) not an RCT (n=103); (6) *in vitro* studies (n=1); (7) no interesting or incomplete outcomes (n=50). Ultimately, 11 studies studies[8-10,18-25] that included 2,248 patients were selected for the systematic review and meta-analysis.

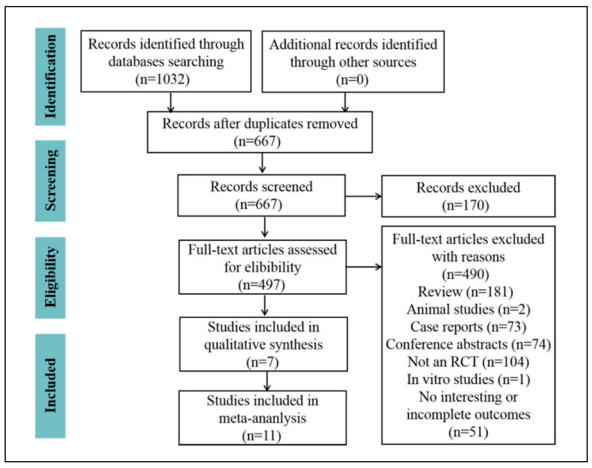

Figure 1. Flowchart of studies evaluating qualified research through selection process.

Study Characteristics

The details of the baseline populations' characteristics, average age, study period, sample size, diagnosis, and drug interventions of 11 eligible trials are shown in Table I. The study period ranged from 2016 to 2020. Of the included studies, 8 investigated lung cancer, the other 3 studied colorectal cancer, esophageal cancer, and hepatocellular carcinoma, respectively. Additionally, the combined treatment therapies included chemotherapy drugs (7 articles) and targeted drugs (4 articles). The chemotherapy drugs used in the enrolled studies were gemcitabine, platinum, pemetrexed, irinotecan, capecitabine, and albumin paclitaxel. The targeted drugs of anlotinib, apatinib, and bevacizumab biosimilar were included.

Clinical Efficacy Response

All studies included in the analysis reported the efficacy response of combined treatment with sintilimab. A fixed effects model was used according to the I^2 value. The results of the meta-analysis of ORR, CR and DCR of sintilimab combination therapy were better than single treatment [RR=1.39, 95% CI (1.19, 1.62), p<0.001; RR=2.65, 95% CI (1.52, 4.61), p<0.001; RR=1.36, 95% CI (1.23, 1.50), p=0.001] (Figure 2).

PFS and OS

There were 7[8-10,19,20,24,25] and 3[10,18,19] articles studying the effects of sintilimab combinations on the PFS and OS, respectively. The pooled results indicated that both sintilimab plus chemotherapy and sintilimab plus targeted therapy prolonged PFS [HR=0.56, 95% CI (0.43, 0.69), p<0.001; HR=0.56, 95% CI (0.49, 0.64), p <0.001]. Meanwhile, an improvement was found for OS in sintilimab combination group as compared to single treatment group [HR=0.59, 95% CI (0.48, 0.70), p <0.001] (Figure 3).

Subgroup Efficacy Analysis

In order to evaluate the efficacy of different combined regimens, the subgroup analyses were conducted. In terms of different combination therapies, it was indicated that both sintilimab

Table I. Characteristics of included studies.

Study ID	Study period	Sample size	Age	Diagnosis	Intervention
Liang et al[18]	2016.01-2020.01	60/60	51-76	Advanced NSCLC	Sintilimab + gemcitabine + platinum *vs*. gemcitabine + platinum
Yang et al[8]	2018.08-2019.07	266/131	18-75	Nonsquamous NSCLC	Sintilimab + pemetrexed + platinum *vs*. pemetrexed + platinum
Zhou et al[9]	2018.09-2019.07	179/178	18-75	Locally advanced or metastatic sqNSCLC	Sintilimab + pemetrexed + platinum *vs*. pemetrexed + platinum
Yang et al[19]	-	266/131	-	Nonsquamous NSCLC	Sintilimab + pemetrexed + platinum *vs*. pemetrexed + platinum
Cai et al[20]	2018.01-2020.07	42/40	18-75	Advanced colorectal cancer	Sintilimab + irinotecan + capecitabine *vs*. irinotecan + capecitabine
He et al[21]	2018.01-2020.12	35/35	35-75	NSCLC IV	Sintilimab + albumin paclitaxel *vs*. albumin paclitaxel
Li et al[22]	2019.02-2020.02	61/63	≥ 18	Advanced Lung adenocarcinoma	Sintilimab + pemetrexed + cisplatin *vs*. pemetrexed + cisplatin
Chen et al[23]	2018.01-2018.12	15/15	18-75	Advanced or metastatic NSCLC	Sintilimab + anlotinib hydrochloride *vs*. Sintilimab;
Chen et al[24]	2018.01-2019.01	29/29	-	Advanced NSCLC	Sintilimab + anlotinib hydrochloride *vs*. Sintilimab;
Liang et al[25]	2019.01-2020.03	21/21	18-75	Advanced esophageal cancer	Sintilimab + apatinib *vs*. apatinib
Ren et al[10]	2019.02-2020.01	380/191	≥ 18	Unresectable hepatocellular carcinoma	Sintilimab + bevacizumab biosimilar *vs*. sorafenib

NSCLC: non-small cell lung cancer; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kin.

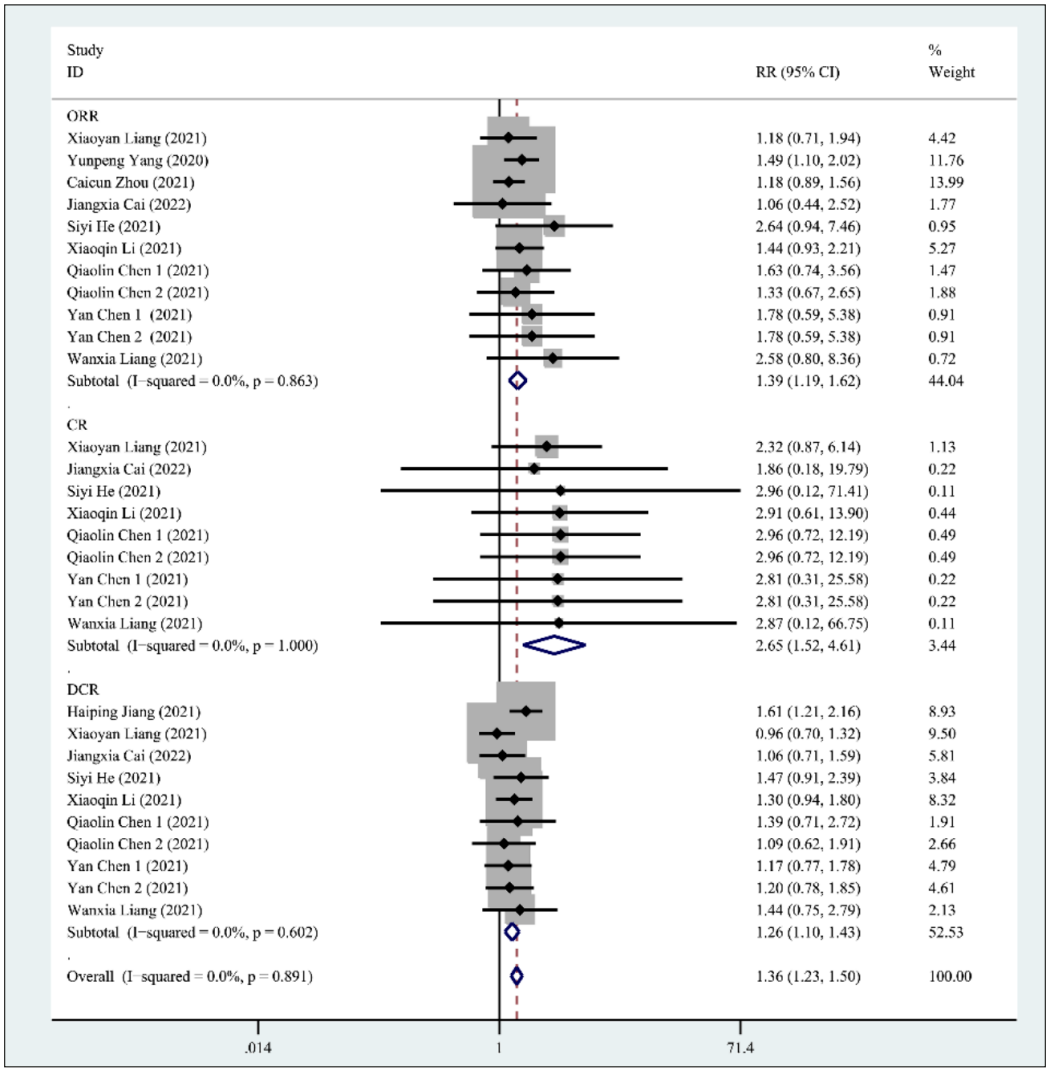

Figure 2. Forest plot for completion response (CR), objective response rate (ORR), disease control rate (DCR) that compared sintilimab combinations with single treatment in tumors.

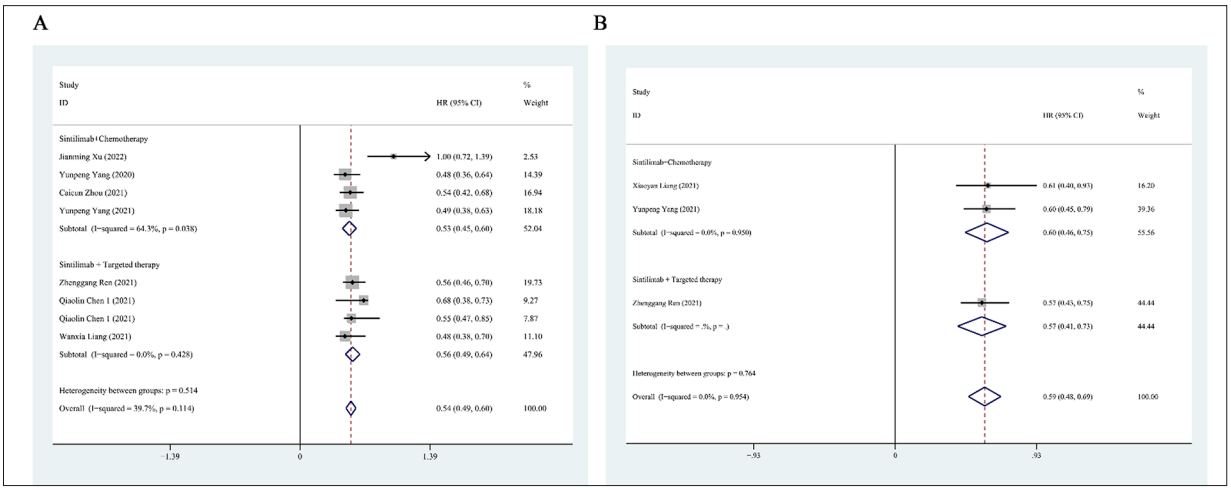

Figure 3. Forest plot for progression- free survival (PFS) (**A**) and overall survival (OS), and that compared sintilimab combinations with single treatment in tumors (**B**).

plus chemotherapy and sintilimab plus targeted therapy had a better ORR [RR=1.34, 95% CI (1.13, 1.59), p=0.001; RR=1.70, 95% CI (1.13, 2.56), p=0.011] and CR [RR=2.44, 95% CI (1.14, 5.20), p=0.021; RR=2.91, 95% CI (1.29, 6.57), p=0.010] compared to single treatment (Figure 4). Meanwhile, sintilimab plus chemotherapy had a better DCR than single treatment, while no difference was found between sintilimab plus targeted therapy and single treatment (RR=1.27, 95% CI (1.09, 1.48), p=0.003; RR=1.23, 95% CI (0.97, 1.55), p=0.083) (**Supplementary Figure 1**). In terms of different tumor types, there were significant improvements of ORR, CR and DCR in lung cancer patients, while no significant difference in esophageal cancer patients. Additionally, prolonged PFS was found in different tumor types including lung cancer, esophageal cancer, and hepatocellular carcinoma (**Supplementary Figure 2**).

Safety Analysis

The most common AEs (incidence ≥ 20%) were anemia, decreased neutrophil count, decreased white blood count, decreased platelet count, nausea, decreased appetite, ALT increased, vomiting, AST increased, Asthenia and constipation. The most frequent AEs of grade 3 or worse were anemia, decreased neutrophil/white blood cell/platelet counts (Table II). The meta-analysis of the incidence of any grade and grade 3 or worse AEs were performed. There was no significant heterogeneity between the studies, and the fixed effects model was adopted. The results of meta-analysis suggested that there was no significant difference in incidence of any grade and grade 3 or worse AEs between sintilimab combination therapies and single treatment [RR=1.00, 95% CI (0.91, 1.10), p=0.991; RR=1.06, 95% CI (0.94, 1.20), p=0.352] (Figure 5).

Additionally, only two studies distinguished the treatment-related adverse events and irAEs. The results demonstrated that the incidence rate of irAEs of any grade or grade ≥3 was 42.5% *vs.* 45.5%, 5.8% *vs.* 7.7% for sintilimab plus chemotherapy and chemotherapy alone, respectively. The irAEs including rash (8.5% *vs.* 5.3%), hypothyroidism (8.3% *vs.* 5.3%), hyperthyroidism (3.8% *vs.* 2.4%), AST increased (3.6% *vs.* 3.3%), diarrhea (3.6% *vs.* 3.3%), ALT increased (3.4% *vs.* 3.3%), immune-mediated pneumonitis (3.4% *vs.* 1.0%) were chosen ≥3% in either study arm (Table III). Our results indicated that the incidence of any grade irAEs was higher with sintilimab combination as compared to single treatment (RR=1.24, 95% CI (1.01, 1.54), p=0.044), but with no significant differences of grade 3 or worse irAEs (RR=1.11, 95% CI (0.60, 2.03), p=0.741) (Figure 5).

Predictive Role of Potential Factors on PFS

Subgroup analyses of PFS were carried out according to multiple potential factors (age, gender, EGOS PS, PD-L1 expression, smoking status, clinical stage) to investigate the potential effects (Table IV). Our results suggested that across most subgroups that were analyzed, the sintilimab combinations exhibited a superior PFS benefit than the single treatment. Particularly for

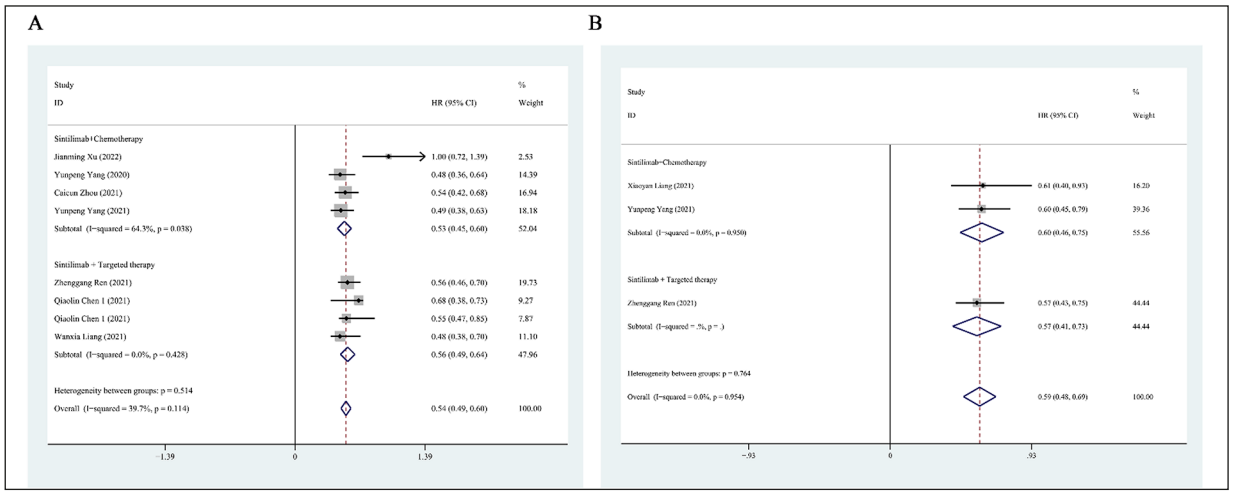

Figure 4. Subgroups analysis of objective response rate (ORR) (**A**) and completion response (CR) based on combined treatment (**B**).

Table II. Treatment-related adverse events (AEs) reported in the patients between sintilimab plus chemotherapy and chemotherapy alone group.

AEs	Sintilimab + Chemotherapy		Chemotherapy	
	Any grade (%)	Grade ≥ 3 (%)	Any grade (%)	Grade ≥ 3 (%)
Anemia	66.4	18.2	84.6	24.4
Decreased neutrophil count	66.4	34.1	81.1	41.7
Decreased white blood count	61.9	19.0	76.0	27.2
Decreased platelet count	47.6	20.6	59.0	30.1
Nausea	40.0	1.3	54.2	0.3
Decreased appetite	28.8	0.2	30.1	1.0
ALT increased	28.5	0.2	32.1	1.3
Vomiting	27.9	1.1	40.1	1.3
AST increased	27.7	0.4	27.6	0.3
Asthenia	26.8	0.9	32.7	1.3
Constipation	23.0	0.0	27.9	0.0
Decreased weight	10.4	0.4	15.1	1.0
Pyrexia	9.5	0.4	15.1	0.0
Hypoalbuminaemia	9.5	0.0	7.1	0.0
Rash	9.3	0.7	8.7	1.0
Infectious pneumonitis	7.3	4.6	9.0	5.4
Hypophagia	5.1	0.2	4.8	0.3
Hemoptysis	4.9	0.5	7.1	1.0
Fatigue	4.9	0.0	9.3	0.0
Hyponatremia	4.7	2.0	10.6	2.9
Proteinuria	2.2	0.0	1.9	0.0
Hypothyroidism	1.3	0.0	0.3	0.0
Decrease in hemoglobin	0.9	0.0	1.3	0.0

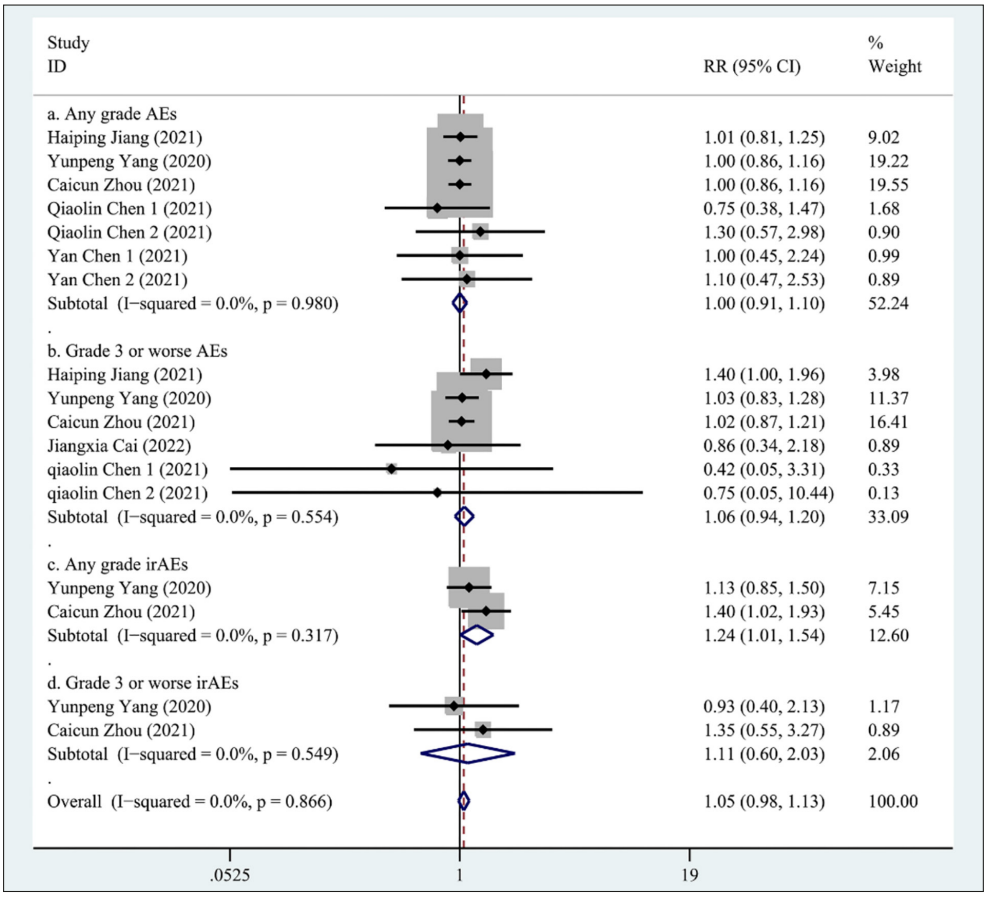

Figure 5. Forest plot for any grade adverse effects (AEs), grade 3 or worse adverse events (AEs), any grade immune-related adverse effects (irAEs), grade 3 or worse irAEs that compared sintilimab plus chemotherapy with sintilimab or chemotherapy alone in solid tumors.

Table III. Immune-related adverse events (irAEs) reported in the patients between sintilimab plus chemotherapy and chemotherapy alone group.

irAEs	Sintilimab + Chemotherapy		Chemotherapy	
	Any grade (%)	Grade ≥ 3 (%)	Any grade (%)	Grade ≥ 3 (%)
Any irAE	42.5	5.8	45.5	7.7
Rash	8.5	0.9	5.3	1.4
Hypothyroidism	8.3	0.0	5.3	0.0
Hyperthyroidism	3.8	0.0	2.4	0.0
AST increased	3.6	0.0	3.3	0.0
Diarrhea	3.6	0.0	3.3	0.0
ALT increased	3.4	0.0	3.3	0.0
Immune-mediated pneumonitis	3.4	0.4	1.0	0.5
Pruritus	2.9	0.0	3.3	0.0
Increased thyroid stimulating hormone	2.9	0.0	1.4	0.0
Decreased thyroid stimulating hormone	2.0	0.0	1.4	0.0
Pyrexia	1.8	0.0	1.9	0.0
Increased amylase	1.8	0.7	4.8	0.0
Blood creatinine increased	0.9	0.0	0.5	0.5
Increased free thyroxine	0.7	0.0	1.9	0.0
Blood thyroid stimulating hormone increased	0.7	0.0	1.9	0.0
Platelet count decreased	0.4	0.0	2.4	1.0

PD-L1 expression, the PFS benefiting from the sintilimab combination was observed in all subgroups of PD-L1 TPS (tumor proportion score), including in patients with TPS less than 1%.

Heterogeneity and Risk of Bias

We assessed the quality of each study (i.e., risk of bias) independently based on the RCT quality evaluation standards of the Cochrane

Table IV. Subgroup analysis of PFS based on age, gender, EGOS PS, PD-L1 expression, smoking status, clinical stage.

Subgroup	HR (95% CI)	*p*-value	Heterogeneity	
			p-value	I^2 value
Age				
≤ 60	0.436 (0.334, 0.538)	< 0.001	0.823	0%
> 60	0.561 (0.457, 0.664)	< 0.001	0.932	0%
Sex				
Male	0.472 (0.395, 0.549)	< 0.001	0.566	0%
Female	0.616 (0.381, 0.850)	< 0.001	0.982	0%
EGOS PS				
0	0.488 (0.321, 0.656)	< 0.001	0.709	0%
1	0.506 (0.419, 0.592)	< 0.001	0.959	0%
PD-L1 expression				
< 1%	0.588 (0.436, 0.740)	< 0.001	0.852	0%
≥ 1%	0.435 (0.354, 0.516)	< 0.001	0.395	0%
1-49%	0.572 (0.367, 0.777)	< 0.001	0.583	0%
≥ 50%	0.363 (0.245, 0.480)	< 0.001	0.236	28.8%
Smoking Status				
Former/Current	0.472 (0.389, 0.555)	< 0.001	0.663	0%
Never	0.574 (0.402, 0.745)	< 0.001	0.975	0%
Clinical Stage				
IIIB/IIIC	0.295 (0.142, 0.447)	< 0.001	0.031	78.4%
IV	0.479 (0.449, 0.508)	< 0.001	0.985	0%

review manual (Figure 6). Information on random sequence generation, assignment hiding, blinding, incomplete outcome data, and selective reporting was collected from each study. If all parameters had information, the study was assigned as low bias. If there was no information, the study was described as highly bias. In information part or ambiguous research, bias risk was defined as unclear. According to our results, 1 study didn't describe the method of randomization. Besides, 2 studies mentioned the allocation was adequately concealed and 3 studies had information regarding blinding. Asymmetry can be found in funnel plots of ORR and PFS, while symmetry existed for CR and AEs (**Supplementary Figure 3**).

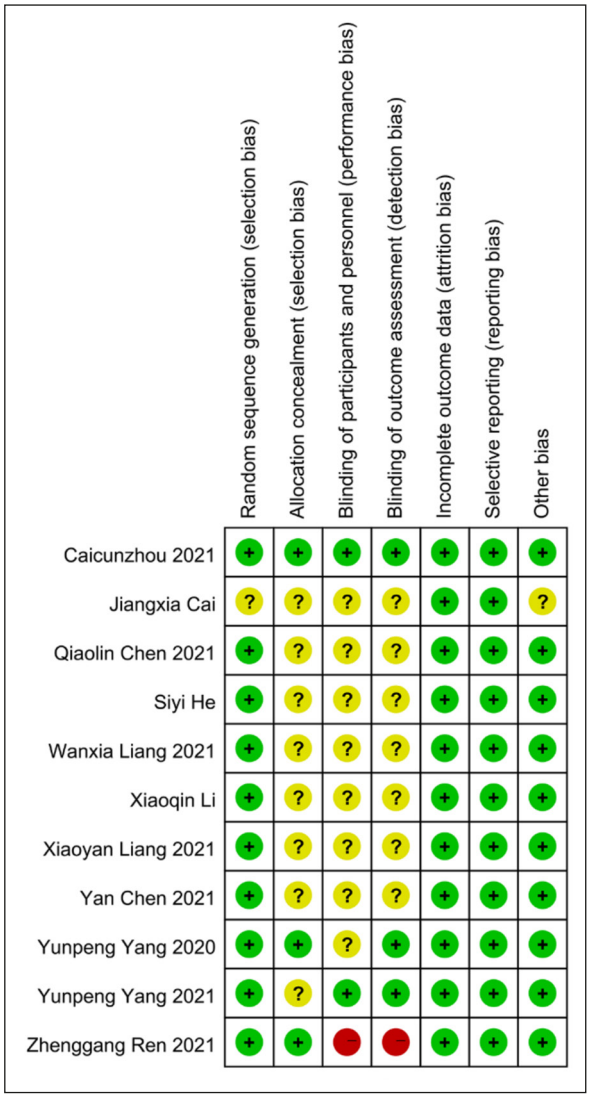

Figure 6. Summary chart of bias risk.

Discussion

Immunotherapy with PD-1 inhibition is a promising therapy in cancer treatment in recent year[26]. To the best of our knowledge, this is the first meta-analysis that includes evidence from RCTs on comparing the efficacy and safety of sintilimab combinations *vs.* single treatment and evaluated the prognostic effects of the biomarker candidates including PD-L1 expression on cancer patients. Our results demonstrated that both sintilimab plus chemotherapy and sintilimab plus targeted therapy could significantly improve ORR and CR, as well as prolong PFS and OS comparing to single treatment. Subgroups of PFS on age, gender, EGOS PS, PD-L1 expression, smoking status, clinical stage all showed sintilimab combination groups exhibited superior PFS benefits than the single treatment group. Additionally, there was no significant difference of AEs incidence rate between two groups. While a higher incidence rate of any grade irAEs was found in sintilimab chemotherapy combination than chemotherapy alone but with no difference of grade 3 or worse irAEs, which were known toxicities and controllable[27]. Overall, our analysis summarized comprehensively to suggest that sintilimab plus chemotherapy or targeted therapy were better than single treatment with acceptable AEs.

PD-1 signaling is commonly hijacked by cancer cells to escape immune surveillance. Although PD-1/PD-L1 therapy have strong anti-tumor effects in some patients, most patients can't benefit from PD-1/PD-L1 therapy due to primary or acquired drug resistance[28]. The combination strategy is considered to be a rational and feasible method to achieve the best therapeutic effect. Currently, the combination of chemotherapy and PD-1/PD-L1 has become a standard treatment for some cancer patients, and many ongoing clinical trials are explored to evaluate the efficacy and safety[4].

Sintilimab is a potent selective anti-PD-1 antibody, which can inhibit the interaction between PD-1 and its ligand. As compared to nivolumab and pembrolizumab, a different binding epitope and greater binding affinity to PD-1 was found for sintilimab[29]. Currently, sintilimab has been approved by NMPA as first-line treatment for locally advanced or metastatic nonsquamous NSCLC in combination with pemetrexed and platinum and advanced or metastatic squamous NSCLC in combination with platinum and gem-

citabine[8,9,19]. Besides, other combination chemotherapeutics such as albumin-bound paclitaxel plus S-1, S-1 and oxaliplatin (SOX), paclitaxel plus cisplatin, irinotecan plus capecitabine were performed to evaluate the efficacy in stage IIIC gastric cancer[30], nasopharyngeal carcinoma[31], esophageal squamous cell carcinoma[32,33]. Strategies that combine other types of immunomodulators and molecular targeted treatments either *in vivo* or *in vitro* are ongoing[29]. However, whether sintilimab combination therapy is more effective and safer still needs to be explored. In our study, we found that both sintilimab plus chemotherapy and sintilimab plus targeted therapy exhibited improvements for ORR, CR, PFS and OS compared to single treatment, which was particularly existed in lung cancer patients (Figure 2-4, **Supplementary Figure 2**). These results indicated that the combination therapy of sintilimab was more effective than single treatment.

Biomarkers are considered as effective tools for patient selection in the response to treatments. It still lacks effective biomarkers to select patients who can benefit from immune combination treatment[34]. Although a large number of studies[19,35,36] have suggested that TMB and PD-L1 expression can be potential biomarkers. Nevertheless, PD-L1 expression and TMB have restricted predictive value. Previous studies[5,37,38] have indicated that improvements of OS and PFS were found for PD-1 inhibitors (such as pembrolizumab) plus chemotherapy treatment in patients with metastatic NSCLC, regardless of PD-L1 expression. Similarly, PFS and OS benefits were also found in patients with low TMB in KEYNOTE-189 and KEYNOTE-407 studies[39,40]. In our involved studies containing NCT03607539, ORIENT-11 and ORIENT-12, the PFS benefit from the sintilimab combination was observed in all subgroups of PD-L1 TPS (tumor proportion score), including in patients with TPS less than 1%, the greatest benefit was found in the subgroup in which the PD-L1 TPS was more than 50%[8,9,19]. Anyhow, the number of involved studies was limited, and it would be speculative to make a conclusion. Interestingly, it was reported that MHC class II pathway was the key to obtain clinical benefits of combined immunotherapy. In the ORIENT-11 study[19], patients with high MHC class II expression who were either low or negative PD-L1 expression had PFS benefit from the sintilimab plus chemotherapy treatment. However, no improvements of clinical outcome were found in those patients with low PD-L1 and MHC class II expression. These findings suggests that it is necessary to develop a composite biomarker including PD-L1 and MHC class II expressions for expanding the patient population.

Not only effectiveness but also safety is of concern when using sintilimab combination therapy in solid tumors. ICIs activate the immune system of cancer patients and promote the killing effect of T cells *in vivo*. Excessive activation of the immune system will lead to the production of irAEs in the human body[41]. Studies[42] have indicated that irAEs occurred more frequently when immunotherapy was added to chemotherapy. The common irAEs included fatigue, skin pruritus, diarrhea, aspartate aminotransferase increase, hypothyroidism, hyperthyroidism and nausea[27], which was consistent with our results. Although there were many kinds of AEs caused by PD-1, compared with chemotherapy, the irAEs symptoms of PD-1 inhibitors were lighter and controllable, resulting in lower treatment interruption rate and different coverage, mostly manifested in endocrine diseases, skin toxicity and gastrointestinal reactions, while chemotherapy AEs was mainly manifested in hematotoxicity and neurotoxicity[43,44]. For instance, patients who had received sintilimab combination therapy had a higher risk of developing irAEs including rash, hypothyroidism and proteinuria (mainly mild reactions of grade I to II) compared with the patients who received chemotherapy alone[8]. Our results suggested that the overall incidence of any grade and grade 3 or worse AEs in sintilimab combination therapy was a little higher than single drug therapy, but with no significant difference. Specifically, the events of any grade irAEs occurred more in sintilimab combination therapy than single drug therapy, while no significance was found in events of grade 3 or worse irAEs (Figure 4), which was similar to the previous study focused on pembrolizumab plus chemotherapy versus chemotherapy alone for NSCLC[45]. In a word, the irAEs of sintilimab combination therapy were controllable, and consistent with known toxicities.

Limitations

Although this study provided important information regarding the efficacy and safety as well as predictive biomarkers of sintilimab combination therapy for solid tumors, the study had several limitations. Firstly, not all included studies had a large sample size, which might undermine the statistical power of the meta-analysis. Second,

there were differences in the chemotherapeutic or targeted agents between trials, which might impair transitivity and consistency of the results of this meta-analysis. Additionally, the number of involved studies was limited, the predictive value of TMB and MHC class II were not performed. Meanwhile, although the subgroups of PD-L1 expression was conducted, the data was immature to make a conclusion.

Conclusions

This study summarized all of the current evidence, and, to the best of our knowledge, is the first meta-analysis-to date-that compared the efficacy and safety of sintilimab combination therapy and single treatment, as well as evaluating the predictive value of PD-L1 expression. Our results suggested that sintilimab combinations improved CR, ORR, DCR, PFS and OS compared to singe treatment in cancer patients, at the cost of greater but manageable irAEs. PD-L1 expression may not act as a predictive biomarker to select the patients who can benefit from sintilimab combinations. The development of composite biomarkers consisting of PD-L1 and MHC class II expression to enlarge the patient population that benefits from sintilimab combination is worth to be explored.

Conflict of Interest

The authors declare that they have no conflict of interests.

Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Authors' Contribution

J. Li and Z. Dai designed the study. J. Li and X.-Y. Zang performed literature search, analyzed, interpreted the data and drafted the manuscript. Z. Dai revised the draft. All authors had full access to all data, critically revised the paper, approved the final analysis, and took responsibility for all aspects of the work.

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